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INCIDENCE OF ACUTE CORONARY ARTERY OCCLUSION

A DISCUSSION OF THE FACTORS RESPONSIBLE FOR ITS INCREASE

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IT HAS become inescapably clear that heart disease has been, since 1912, the chief cause of death in this country.[1-4] In 1942 almost 400,000 persons died of cardiac disease alone, about 28.5 per cent of all deaths.[2] It is probable that at least 4,000,000 persons are afflicted with heart disease. One survey gives an estimate of double this figure, placing the total at 8,000,000.[5]

PREVALENCE OF CORONARY ARTERY DISEASE

In any analysis of cardiac disease, the increase in coronary artery disease that has taken place during the last thirty years is especially striking. It has become the most important of the heart diseases. In 1942, deaths throughout the country from diseases of the coronary arteries and angina pectoris attained the highest figure on record, 113,636.[2] Coronary artery disease is thus the cause of 8.5 per cent of all deaths, the most common cause of mortality in this country with the exception of cancer. According to Clawson,[6] 30 per cent of patients with organic heart disease have coronary artery involvement. Levy, Bruenn, and Kurtz[7] give a percentage of 25.9. White[8] estimates a figure of 37 per cent. *Vital Statistics of the United States, 1942*, report 30 per cent.[2] From these figures, it would appear that coronary artery disease comprises about one-third of all heart ailments. That this proportion is probably a conservative one is emphasized by a necropsy study in 1937 and 1938 of patients who died of heart disease in a large hospital in New York.[9] Fifty-four per cent of the deaths were

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attributable to disease of the coronary arteries. In this institution, every effort was made to determine accurate diagnoses during post-mortem examination of the heart; it seems reasonable to predict that this percentage will be corroborated in future examinations.

PREVALENCE OF ACUTE CORONARY ARTERY OCCLUSION

Figures on the prevalence of acute coronary artery occlusion cannot be obtained from the United States Census reports or, in fact, from any other source. The Census has no specific listing for acute coronary occlusion or thrombosis; it lists only diseases of the coronary arteries and angina pectoris. Unfortunately, even mortality due to the latter is not properly recorded, because in the *Manual of the International List of Causes of Death and Joint Causes of Death*,[10] one disease is given greater weight than another. "Myocarditis" takes precedence over coronary artery disease and hence, as Hedley[11] points out, if the death certificate carries the diagnosis of "myocarditis and acute coronary thrombosis," the death is recorded as myocarditis, even though the attending physician may have considered it due to acute coronary thrombosis. Similarly, "nephritis" is given precedence over coronary disease. Hedley's investigation revealed that in 259 death certificates in which acute coronary thrombosis was diagnosed as the cause of death (in 144 as primary and in 115 as secondary), the official tabulation ascribed death to involvement of the coronary artery in only seventy-eight instances.

Since official records do not afford accurate statistics on the subject, information must be sought from other sources if we are to have a true picture of the incidence of acute coronary artery occlusion or thrombosis. In 1939, my colleagues and I[12] worked out a basis for computing the occurrence of these diseases. The figures that we presented at that time will be now brought up-to-date and some significant additions will be made.

In sampling death certificates of the state of New York,* it was observed that at least 25 per cent of the deaths reported in the *Manual of the International List of Causes of Death and Joint Causes of Death* under "Diseases of the Myocardium (Not Rheumatic)" were instances of acute coronary artery occlusion and that at least 60 per cent of the deaths ascribed to "coronary disease" and 80 per cent of those attributed to "angina pectoris" were instances of acute coronary occlusion. Assuming that these percentages hold good for the whole country, the number of cases of acute coronary occlusion in the United States for 1942 may be calculated. During 1942, there were 200,851 deaths from diseases of the myocardium (excluding rheumatic), 107,273 from diseases of the coronary arteries, and 6,363 from angina pectoris.[13] Multiplying these figures by 25, 60, and 80 per cent, respectively, the total number of deaths from acute coronary occlusion was 119,666, or practically 120,000.

The figure of 120,000 deaths in 1942, the result of acute coronary artery occlusion, is truly conservative. Deaths listed under the headings "Other

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Diseases of the Heart (Not Rheumatic)" and "Functional Diseases of the Heart" (Numbers 95c and 95a, respectively, in the *Manual of the International List of Causes of Death and Joint Causes of Death*) were not included in our sampling, and many of these were probably cases of acute coronary occlusion.

Assuming that the mortality rate for acute coronary artery occlusion is 20 per cent, 120,000 deaths indicate that 600,000 attacks occurred in 1942. If a mortality rate of 15 per cent is chosen, then the incidence of attacks is 800,000, a figure that is, I believe, nearer the truth.

Since acute coronary occlusion is chiefly a disease of persons over 40 years of age, its incidence in individuals over this age is of interest. Approximately 34 per cent of the people in this country are in the age group over 40 years; that is, 23,000,000 men and about the same number of women. However, coronary disease is more common in men than in women. In recent clinical investigations,[14] the ratio was about 3.5 to 1, whereas the Census tallies[2] indicate that the number of male deaths from coronary artery disease is not quite 2.5 times as many as the number of female deaths. Taking an average of 3 to 1, we find that of 800,000 attacks, 600,000 will occur in men and 200,000 in women. This means that every year, roughly 1 man in 38, 40 years of age and over, and 1 woman in 115, in the same age group, sustain closure of a coronary artery. If the incidence of acute coronary artery occlusion is accepted as 600,000, then the incidence becomes roughly 1 man in 50 and 1 woman in 150.

To the objection that, because of World War II, 1942 is not as representative a year as 1941, let me say that the United States Census figures for both years are practically the same.[13] In 1942, the number in the Armed Force overseas was not large. Furthermore, the United States Census often takes into consideration troops overseas.[13]

Mortality Rate in Acute Coronary Occlusion.—Recent reports[15-18] indicate that duration of life following acute coronary occlusion is much longer than it was earlier believed to be. Early reports described mortality rates of from 35 to 65 per cent in acute coronary occlusion.[15,19,20,21] Since 1930, the figures have been much lower. Conner and Holt,[15] in 1930, indicated that the rate might be as low as 16 per cent in first attacks. My colleagues and I,[16] in a series of 267 cases, found that the rate for all cases was 16.5 per cent, and only 8 per cent in first attacks. Levine[22] recently quoted rates of 15 to 25 per cent. It must be remembered that the most seriously ill patients, among whom the death rate will be high, are observed in the wards of hospitals, and most of the published reports are based on hospital records. Patients not so ill are more often seen at home. I believe that if all cases of acute coronary artery occlusion were reported, the mortality rate would prove to be less than 20 per cent, and, for the first attack, less than 10 per cent.

INCREASE IN CORONARY DISEASES

Increase in the prevalence of coronary artery disease, and more particularly acute coronary occlusion, is attributable to (1) lengthened span of life, (2) ageing

of the population, (3) improved diagnosis and treatment, and (4) accuracy in terminology.

Lengthened Span of Life.—The principal factor underlying the increase in coronary disease is the lengthening span of life which has taken place, notably in the past fifty years.

According to Dublin and Lotka,[23] the citizens of Rome in its halcyon days enjoyed a life span of but twenty to thirty years. In the beginning of the nineteenth century, "an average length of life of thirty-five to forty years may have been common in various localities among civilized nations."

Among Metropolitan Life Insurance industrial policyholders,[24] the life span between 1912 and 1944 has increased almost eighteen years and, since the decade 1879 to 1889, thirty years (Table I).

TABLE I. INCREASE IN LIFE SPAN BETWEEN THE YEARS 1879 AND 1944

YEAR	LIFE SPAN (YR.)
1879-1889	34.00
1911-1912	46.63
1919-1920	51.14
1930	57.36
1940	62.93
1944	64.40

How has the span of life been so augmented that it has almost attained the Biblical three score and ten? First, there has been a significant reduction in infectious disease.[2] The pneumonia and influenza death rate in 1900, per 100,000 population, was 202; in 1942, it had dropped to 55.7. In the same interval, the tuberculosis rate had fallen from 174.5 to 39.6; diarrhea and enteritis, from 142.7 to 8.8; diphtheria, from 40.3 to 1.0; typhoid and paratyphoid, from 31.5 to 0.6; whooping cough, from 12.2 to 1.9; scarlet fever, from 9.6 to 0.3.

New drugs are affording invaluable aid in controlling diseases that heretofore carried a high mortality. The figures in Table II, cited by Morgan,[25] show the role played by the sulfonamide drugs and penicillin in World War II.

TABLE II. COMPARISON OF FATALITIES IN WORLD WAR I AND WORLD WAR II

DISEASE	FATALITY IN PER CENT	
	WORLD WAR I	WORLD WAR II
Meningitis	38.0	4.0
Pneumonia	28.0	0.7
Tuberculosis	17.3	1.8
Dysentery	1.6	0.05

This dramatic reduction in infectious disease will continue with the increasing use of the sulfonamides and penicillin, and particularly of streptomycin. Streptomycin, it appears, will help to counteract the diseases now considered resistant to the sulfonamide drugs and to penicillin; for example, typhoid and tuberculosis.

Advance in medical knowledge with its improvements in surgical and medical treatment of disease as well as in diagnosis has saved the lives of millions of people, thus increasing the life span. The prophylactic measures taken by the Army to prevent and control such diseases as malaria, tetanus, typhoid, typhus, and cholera practically eliminated these formerly devastating diseases.

Progress in public health and sanitation, particularly in the fields of water and milk supply, disposal of sewage and waste, and nutrition, has contributed largely to reduction of infectious diseases. Nutritional diseases, such as pellagra, rickets, scurvy, and beriberi, have been brought under control. Improved ventilation and heating in factories and workshops have also made their contribution to longer life.

Ageing of the Population.—Growth in size of the older age groups in the population is another cause for the greater frequency with which coronary artery disease has been observed in recent years. In the United States in 1850, 8.9 per cent of the people were 50 years of age and older; in 1930, the rate had risen to 17.2 per cent.[26] According to the National Resources Planning Board,[26] there were, in 1900, 8,500,000 persons between the ages of 50 and 74; in 1940, 24,000,000; and in 1980, there will be 42,000,000. As we have seen, it is in this older age group that two-thirds of the episodes of acute coronary occlusion occur. Another factor in the ageing of the population has been the decline in birth rate of this country.

Improved Diagnosis and Treatment.—Previous to the publication of Herrick's reports in 1912, 1918, and 1919,[27-29] acute coronary occlusion had not been recognized as a specific cardiac condition. Today, thanks to Herrick, Levine, and Tranter,[30] Libman,[31,32] Pardee,[33] Smith,[34] Wolferth and Wood,[35] Wilson and colleagues,[36] Parkinson and Bedford,[37] and others, the clinical diagnosis of acute coronary occlusion is as well-defined as that of acute appendicitis.

The electrocardiogram is a potent aid in the diagnosis of acute coronary artery occlusion. It will often demonstrate acute coronary occlusion when the condition is not suspected or when the diagnosis is in doubt. "Acute indigestion," gall bladder disease, pneumonia, and stomach ulcer are much less frequently mistaken for acute coronary occlusion than they used to be.

The x-ray machine, the kymograph,[38] and the fluoroscope[39] are additional aids in the diagnosis of coronary disease.

Advances in medical knowledge have resulted not only in early recognition of acute coronary artery occousion, but also in more effective methods of treating patients with this condition. With insistence on immediate bed rest,[27] avoidance of overtreatment with drugs, and a low calorie intake,[16,40,41] early in the attack, the mortality rate has fallen. These preventive measures have not given the dramatic results that have followed the introduction of new drugs in infectious diseases, but they have saved untold numbers of lives; I take pride in

having been a pioneer in this newer treatment of acute coronary artery occlusion. Not long ago, patients suffering an attack of acute coronary occlusion received powerful drugs almost routinely: digitalis and often adrenalin, strychnine, and camphor. Although extremely ill, the patient was given a "cardiac diet," which consisted of 3,000 to 4,000 calories, with emphasis on carbohydrates because the specialized conduction tissue of the heart was believed to contain much glycogen.

Accuracy in Terminology.—The terms "coronary" disease and "angina pectoris due to coronary disease"[42] have replaced such obsolete and vague expressions as "myocarditis," "cardiac dilatation," "heart failure," "chronic cardiac," "dropsy," and "senility." Since these ambiguous diagnoses have disappeared and definitive diagnoses have come into use, records show an automatic increase in the frequency of coronary disease.[11]

DISCUSSION

If we turn to the older statistics and compare them with recent ones, there has been an apparent startling increase in coronary disease. From the year 1930, the gain in disease of the coronary arteries appears phenomenal. Thus, according to United States Census enumerations,[43] there were 28,286 deaths in 1930 from diseases of the coronary arteries and angina pectoris, but in 1940 the figure was 101,463. In the ten-year period 1930 to 1940, the Metropolitan Life Insurance Company reported a doubling in the number of persons suffering from this disease.[44] Dublin and Lotka[23] recorded a "perpendicular rise" from 5.6 per 100,000 in 1930 to 23.1 in 1935, an increment of more than 300 per cent. Denny[45] and also Willius[46] reported a similar amazing growth of coronary disease. It is obvious that the growth in this decade is out of line and cannot be a true increase. It is, of course, explained in part by the fact that previous to 1930, acute coronary occlusion was not too readily recognized, and it was not until 1930 that the disease began to be listed.[1,4,7,47,48,49,50] Ageing of the population is another contributing factor.[51,52] However, the increase in coronary disease, or, specifically, acute coronary occlusion, has been due in large measure to increase in life span, improvement in diagnosis, and more adequate treatment of the patients.

There are many physicians who are still of the opinion that there has been a true increase in coronary disease and cite stress and strain of modern life, anxiety states, abuse of tobacco, and overweight as causative factors.[53] I do not subscribe to this theory. Stress and strain today is not greater than that which existed in ancient times, during periods of wars, great fires, plagues, and famines. In fact, people work shorter hours and in greater comfort. Moreover, our investigations[54-56] have revealed that acute coronary occlusion is not a respector of persons: rich and poor, the laborer, the executive, or the ordinary man at the desk are all possible victims.[54-56]

For many years it has been said that doctors are particularly prone to acute coronary thrombosis.[57] Musser[58] believed that coronary arterial disease was properly called "the doctor's disease." A study of obituaries of physicians as reviewed yearly in the *Journal of the American Medical Association*[59] might lead the unwary to gain this impression, since the numbers dying from this disease appears

at first sight to be large. Those who believe that doctors are especially liable to die of acute coronary thrombosis give as the cause the sedentary nature of their occupation. Yet there are not harder working persons than members of the medical profession. My associates and I have already made a comparison of the occupations of our patients suffering from acute coronary occlusion with the occupations of the population as listed in the United States Census, and the results of our investigation yielded no significant difference in the relative proportions.[54-55] The professional class, including physicians, was represented no more and no less than one would expect from their numbers in the general population. Recently, other authors have examined the question of coronary disease among physicians and reached the same conclusions that we did. Falk[60] believes that the apparent increase in coronary artery disease among doctors is accounted for by "a more accurate diagnostic trend." Fitz[61] estimated the age distribution of American physicians from 1907 to 1942 and found that they, like others, were living longer and that the prevalence of coronary disease among them had risen correspondingly. Levine and Hindle[62] reported that the average age at death of physicians dying from coronary disease did not differ from the average age of lay persons who were victims of this disease. The fact is that physicians who live long enough may sustain acute coronary occlusion but in no greater or lesser numbers than other persons of the same age.[55]

Tobacco is, of course, perennially held responsible for heart disease.[53,63] White and Sharber[64] investigated the relationship of tobacco and alcohol to angina pectoris and concluded that neither played an important role in the genesis of this cardiac disease. Blumer[65] arrived at a similar conclusion in respect to acute coronary occlusion. My associates and I,[54] in an analysis of the histories of 364 patients with acute coronary artery thrombosis, found that one-third of the men and practically all of the women were nonsmokers. As the proportion of heavy and moderate smokers in this group of patients did not differ from the ratio in the general population, it may be assumed that the use of tobacco was not influential in precipitating the attacks of acute coronary thrombosis.

At present, figures showing the incidence of acute coronary thrombosis can at best be only an estimate, but we are approaching closer to the actual facts. But if statistics are to reflect accurately the status of acute coronary occlusion, it must be kept in mind that there is more than one type of arteriosclerotic coronary artery disease; that is, there are *coronary artery diseases* rather than a coronary artery disease.[66] There are, for example, the simple episode of angina pectoris, the acute attack of coronary occlusion, and, finally, myocardial necrosis without occlusion.[67] The importance of distinguishing these types of coronary artery disease cannot be emphasized too strongly, for the next step should be to distinguish sharply between myocardial infarction due to acute coronary occlusion and the myocardial necrosis without occlusion. Their precipitating causes, pathology, electrocardiograms, and treatment differ.[66]

The present high incidence of coronary disease should not be cause for pessimism but rather an impetus to further research. Progress in medicine, public health, and sanitation has brought about a decline in the number of deaths

in infancy, childhood, and even in adult life and in old age. The life span has been lengthened with a concomitant increase in diseases of old age. Yet there is still much knowledge needed if the ill health due to heart disease is to be alleviated. As Dublin[68] said, "No other disease (coronary artery disease) in the entire field of medicine, with the possible exception of cancer, offers so large an opportunity for life-saving service."

Dublin and Lotka,[23] in 1936, hypothesized an eventual expectation of life at birth of 70 years. Of course, after birth this would go beyond 70 years. Piersol[69] surmised that by 1960 a boy might expect to live to 75 years and a girl to 80 years of age or more. With advances in medicine, particularly since the advent of the sulfonamide drugs, penicillin and streptomycin, it is not improbable that arteriosclerotic disease may be delayed and the life span become five score.

SUMMARY

Heart disease is the chief cause of death in the United States. Nearly 400,000 persons die yearly of cardiac disease. This comprises almost 30 per cent of all deaths.

Coronary artery disease alone is the greatest cause of mortality except cancer. Eight and one-half per cent of all deaths result from this condition. Approximately 114,000 persons die annually of coronary disease.

Of cardiac fatalities, those due to coronary disease are estimated to be from 30 to 50 per cent.

Acute coronary occlusion or thrombosis is not listed separately in the Census but is included under "Diseases of the Coronary Arteries" and "Angina Pectoris." The estimation of the actual number of deaths from acute coronary occlusion presented in this paper was made by sampling New York State death certificates and by applying the figures thus derived to the rest of the country. It was computed that at least 25 per cent of deaths reported under "Diseases of the Myocardium," 60 per cent of those ascribed to "Coronary Disease," and 80 per cent of those listed as "Angina Pectoris" were, in fact, instances of acute coronary occlusion. On the basis of these percentages, it is estimated that there were 120,000 deaths from acute coronary occlusion in this country in 1942. If the mortality rate for this disease is accepted as 15 per cent, there are about 800,000 attacks of acute coronary occlusion yearly.

Using the United States Census figures for the number of men and women in this country over 40 years of age, and an incidence ratio of 3 men to 1 woman, we may conclude that approximately 1 man in 40 and 1 woman in 115 experience an attack of acute coronary occlusion yearly. These figures will, of course, vary if other mortality rates are adopted for the computation. There is some evidence that the number of instances of acute coronary occlusion may be as high as 1,000,000; if this figure is accepted, 1 man in 30 and 1 woman in 90, 40 years of age and over, annually sustain acute complete obstruction of a coronary artery.

The increase in diseases of the coronary arteries is explained by the increased span of life brought about by reduction in infectious disease of childhood and adult life, advances in medical knowledge, and improvement in public health

and sanitation. The numbers of persons suffering from coronary disease will continue to increase with the relative increase in older age groups, decline in birth rate, improvement in diagnosis, more effective treatment of coronary disease, and, indirectly, by the use of correct terminology.

The startling increase in incidence of acute coronary occlusion since 1930 is due to better reporting of coronary disease since that year.

There is no evidence that stress and strain of modern life or the use of tobacco or alcohol are factors in the production of disease of the coronary arteries.

Physicians are not more prone to acute coronary occlusion than are other persons. It should no longer be thought of as the "doctor's disease."

With the use of the sulfonamide drugs, penicillin, and streptomycin, the span of life will increase, and, therefore, the incidence of acute coronary disease will continue to rise. This magnitude of the incidence of coronary disease is a challenge to further research.

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COARCTATION OF THE AORTA

A Review of 104 Autopsied Cases of the "Adult Type," 2 Years of Age or Older

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POSSIBLE surgical treatment of coarctation of the aorta[120,122,127,135] stimulated this analysis of autopsied cases that have been collected since Abbott's review in 1928.[119] Causes of death, cardiovascular findings, and conclusions regarding life expectancy are presented.

Coarctation is not a common lesion. The probable incidence of the adult type is 1 per 3,000 or 4,000 or more autopsies. The diagnosis is being made more frequently during the life of the patient because of numerous clinical, radiologic, and physiologic studies.

Most cases may be classified into one of two groups: (1) cases in which the coarctation commonly is accompanied by major congenital cardiac anomalies, the infant not surviving more than days or weeks, and (2) cases in which coarctation is the major or sole anomaly, the patient living over a period of years. In the former group, sometimes called the "infantile" type, the constricted aortic segment usually diffusely involves the entire region of the fetal isthmus (from the origin of the left subclavian artery to the site of insertion of the ductus arteriosus) and the associated serious cardiac anomalies usually preclude normal cardiac function. The latter group, sometimes called the "adult" type, occurs as a more focal area of constriction, usually 1 cm. or less in length, in the same region, most frequently at or just below (rarely above) the insertion of the ligamentum arteriosum. In these cases the effect on the heart and circulation is the result of aortic obstruction. The adult type has been described in infants[159] and the infantile type, in adults. Combined forms occur.

Because this survey was made from the viewpoint of possible surgical treatment, the cases included were of the adult type with moderate, extreme, or complete (atresic) constriction of the aorta. Cases of slight coarctation were omitted as these had circulatory changes which probably were insufficient to make possible an ante-mortem diagnosis. One exception[46] in which such a diagnosis was made was included. Patients less than 2 years of age and those without post-mortem studies also were omitted. A small number of reports could not be

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included because the data were incomplete or the journals were unavailable.[105-117,141] Abbott,[119] using the same criteria, analyzed 200 cases from the time of the earliest report[151] in 1791 to 1928. The 104 cases collected since the latter date form the basis of the present review. Unfortunately, some gross and many microscopic observations were lacking in the majority of these reports.

SEX

Coarctation is about four to five times more common in males than in females. The ratio was approximately 5:1 in this series (87:17) and 4:1 in Abbott's series. There is no evident reason for this preponderance.

AGE

In this series, ages ranged from 3 to 76 years. The adult type has been reported in patients from 6 months[159] to 92 years[154] of age. The average age at death was 35.0 years, a figure comparable to Abbott's data (see Table I). According to causes of death, the average ages varied from 27.7 to 47.0 years. Sixty-one per cent of these patients died before or during the fortieth year of life. Considering the fact that Abbott's series included cases reported over a span of 137 years, during which time life expectancy has increased greatly, it is not surprising that she found that 74 per cent of her patients died before or during the fortieth year of life. The percentages of patients in each age decade in this series is quite similar to the corresponding data presented by Abbott. The majority of the deaths from rupture of the aorta or from an intracranial lesion occurred in the second and third decades, from bacterial endocarditis or aortitis in the first five decades, and from congestive failure in the third to fifth decades. Deaths from incidental causes occurred throughout all decades with a peak in the fifth decade.

CAUSES OF DEATH

Seventy-four per cent of these patients died as a result of rupture of the aorta, bacterial endocarditis or aortitis, congestive failure, or an intracranial lesion. The remaining 26 per cent died of causes which may be considered as "incidental." Approximately the same frequencies of the various causes of death were found by Abbott, although the exact percentages are not stated. The only discrepancy of some magnitude is her observation that 29 per cent of patients died of congestive failure and 16 per cent died of bacterial infection of the heart or aorta. This is understandable when one considers the progress in pathologic recognition of congestive failure and bacterial endocarditis and aortitis during the past century or more.

Incidental Causes.—Included in this group were patients with coarctation who died as a result of pneumonia,[12,33,59,64,95] probable uremia,[47,51,85,88] carcinoma with bacteremia,[82] carcinoma,[13,24] trauma,[4,6,31,49] postoperatively after major surgery,[50,60] pulmonary embolism,[28,34] perforation of a duodenal ulcer,[57] or acute esophagitis.[70] Three patients[5,63,75] died suddenly of coronary artery disease and

TABLE I. DATA PERTAINING TO 104 AUTOPSIED CASES OF COARCTATION OF THE AORTA (ADULT TYPE), TWO YEARS OF AGE OR OLDER

CAUSES OF DEATH	NUMBER OF COARCTATION PATIENTS IN EACH AGE DECADE								TOTAL NUMBER OF PATIENTS	% TOTAL DEATHS (THIS SERIES)	% TOTAL DEATHS (ABBOTT'S SERIES)	AVERAGE AGE (THIS SERIES)	AVERAGE AGE (ABBOTT'S SERIES)	BICUSPID AORTIC VALVES	
	2-10	10-20	20-30	30-40	40-50	50-60	60-70	OVER 70						NUMBER	% ACCORDING TO CAUSE OF DEATH
Incidental	1	3	1	2	**10**	2	6	2	27	25.9	22.5	47.0	?	8	29.6
Rupture of the aorta	1	**8**	**8**	2	3	2	0	0	24	23.1	20.0	27.7	22.2	10	41.7
Bacterial endocarditis or aortitis	**3**	**3**	**7**	**5**	**4**	1	0	0	23	22.1	16.0	28.7	?	14	60.9
Congestive failure	0	1	**3**	**5**	**7**	1	1	0	18	18.3	29.0	39.3	?	8	42.1
Intracranial lesion	0	**3**	**4**	2	1	1	0	0	11	10.6	12.5	28.0	30.1	4	36.4
Total	5	18	23	16	25	7	7	2	103	100.0	100.0	35.0	33.5	44	42.3
% Total deaths (this series)	4.8	17.5	22.3	15.6	24.3	6.8	6.8	1.9							
% Total deaths (Abbott's series)	4.5	22.5	24.5	22.5	14.0	6.0	5.0	1.0							

Abbott[119] estimated the age in 16 of her 200 cases. One case[26] in this series was omitted, as the age was given as "adult."

two others[53,62] died suddenly from unexplained causes. Only 29 per cent of the deaths from incidental causes occurred before or during the fortieth year of life.

Rupture of the Aorta.—Two types of aortic rupture occurred: (1) in the ascending aorta, which was more frequent (19 cases; average age, 30.0 years), and (2) in the descending aorta just distal to the coarctation (5 cases; average age, 19.1 years). No cases of rupture of the area just proximal to the coarctation or of other portions of the thoracic aorta were found. Ruptured mycotic aneurysms were included with the bacterial group rather than in this group. In one instance[3] there was an associated syphilitic aneurysm in the ascending aorta some distance above the point of rupture. The ruptured segment of the aorta most commonly was dilated and occasionally was described as unusually thin or "hypoplastic"; it was rarely of smaller diameter than normal.

Patients with rupture of the ascending aorta had the usual symptoms of dissecting aneurysm. Death resulted from rupture of the aneurysm into the pericardial cavity with resulting hemopericardium. In the five cases with rupture distal to the coarctation, the aorta eroded into a bronchus,[44] into the esophagus,[7,65] into both,[8] or into the left pleural cavity.[57] Rupture almost always was rapidly fatal, although the possibility of survival is indicated by two reports. The first[46] was a report of a man 62 years of age who suffered rupture of the descending aorta just distal to an extreme coarctation, lived twelve days, and then shot himself. The second[104] was the report of a man 45 years of age with an aneurysm dissecting distally from a moderate coarctation, who died nineteen months later from congestive failure. In the latter case the aneurysmal lumen was endothelialized and contained a canalized thrombus. Recovery from ascending aortic dissection occurs rarely, although no such report is included in this series.

It seems probable that aortic rupture is associated with an abnormal vessel wall. Hypertension was present unless the patient was in shock. No correlation could be found between systolic, diastolic, or pulse pressure levels and the incidence of rupture, when these findings were compared in patients who died of aortic rupture and in patients who died of other causes. In the series of 104 cases, dilation was commonly observed in the aorta, especially in the ascending portion and less commonly in the descending portion. The majority of these dilated areas had not ruptured. It is unfortunate that so few complete microscopic studies of the aorta in regions of rupture and below and above the area of coarctation were described. In general, the media appeared somewhat decreased in thickness and showed varying amounts of necrosis or hyaline degeneration, fibrosis, elastic decrease and fragmentation, basophilic appearance, or cystic change. Atheromatosis was common and the vasa vasorum occasionally exhibited narrowing of lumina by intimal and/or medial thickening. Elastic destruction appeared to be the outstanding lesion. A few reports[48,55,76] indicated that the various changes were more marked proximal to the coarctation, although the number is too small to justify conclusions. Microscopic study of a significantly large number of cases might clarify the relative importance of congenital thinning and medial changes due to hypertension or other factors, in the production of aortic dilation and rupture in coarctation.

Bacterial Endocarditis.—In the large majority of cases the aortic cusps, very frequently bicuspid, were affected, although in two instances[40,42] the bacterial vegetations involved only the cusps of the mitral valve. Alpha streptococci were the most frequent infecting organisms. The clinical courses and associated findings were typical of subacute bacterial endocarditis and death resulted in the usual manner. The nature of the valvular destruction usually resulted in marked aortic insufficiency with high pulse pressures, typical murmurs, associated vascular phenomena, and cardiac hypertrophy. There were two cases of aortic vegetations associated with Roger's disease in which bacterial vegetations were present on the interventricular septal defects.[36,94] Two patients were described as also having syphilitic aortitis (not valvular).[29,90] Seventy per cent of the deaths from bacterial endocarditis occurred before or during the fortieth year of life; the ages at death ranged from 3 to 57 years and averaged 31.2 years. In fourteen of the seventeen patients with bacterial endocarditis, the involved valves were abnormal, either congenitally bicuspid (aortic) or the site of previous valvulitis, apparently rheumatic. The valves were not described in further detail in the remaining three cases.[2,41,42] This tendency for bacterial endocarditis to develop on abnormal cusps is illustrated by comparing the incidences of bacterial vegetations on valves described as "normal" (no instance of bacterial endocarditis in thirty-two cases) and on bicuspid or previously damaged valves (fourteen of sixty-two cases; that is, 23 per cent).

Bacterial Aortitis.—Death from this condition, unassociated with bacterial endocarditis, occurred in six patients whose ages varied from 7 to 38 years and averaged 21.7 years. In two instances the vegetations were on the ascending aorta and in the other four, just distal to the area of coarctation. The mechanisms of death were as follows: overwhelming infection,[71] extension to pericardium with acute pericarditis,[66] rupture into pericardial cavity with hemopericardium,[35] hemoperitoneum from rupture of a mycotic mesenteric aneurysm,[10] rupture into the lung,[56] and uremia with marked embolic glomerulonephritis.[9] The symptomatology mimicked that of bacterial endocarditis; death usually occurred suddenly. The gross descriptions of these aortas, exclusive of the vegetations, did not differ from those in which aortitis did not occur. A single case of apparent spontaneous recovery from bacterial aortitis has been reported, with progressive calcification of an aneurysmal dilation of the aorta (possibly mycotic), distal to the coarctation.[149] We have seen a man, aged 28 years, with coarctation, positive blood cultures for alpha streptococci, and malaise and fever following tooth extraction, and no diastolic murmur, who appears cured one year after massive penicillin therapy. Recent back pain and an expansile sensation in the region of a recently developed aortic dilation just distal to the coarctation suggest that this patient's bacterial invasion occurred in this site.

Several patients with bacterial endocarditis had an associated bacterial aortitis of the ascending portion[46] or just distal to the coarctation.[29,54] Two patients who died of other causes (dissecting aneurysm of the ascending aorta[91] and rupture of an intracranial aneurysm,[92] both apparently not mycotic) also had bacterial aortitis just below the coarctation; one also had bacterial endocarditis of the mitral valve.

Congestive Failure.—The most striking feature in the patients who died primarily as a result of congestive failure was the high incidence of associated cardiovascular malformations or lesions which, per se, could cause failure. Of nineteen patients with coarctation who died of congestive failure, only the records of one contained no mention of renal disease, chronic valvular disease, coronary artery disease, or some other definite cardiac abnormality. Twelve patients had chronic valvular disease: aortic stenosis[43,52,103]; aortic stenosis and insufficiency[26]; aortic insufficiency[48,77]; aortic valvular disease[84]; aortic and mitral disease[58,102]; aortic, mitral, and tricuspid stenosis[1]; and valvular disease with acute rheumatic carditis.[22,38] Three additional patients[87,98,99] had chronic valvular and coronary artery disease. One other patient[73] had marked aortic stenosis, coronary artery disease, and arteriolar nephrosclerosis. Another patient, 23 years of age, had extreme coarctation, patent ductus arteriosus, and symptoms suggesting portal cirrhosis for two years. Death occurred six months after a Talma-Morison omentopexy, supposedly from rapidly progressive congestive failure. This patient also had a paroxysmal tachycardia terminally and left bundle branch block.[89] Still another patient,[79] 50 years of age, had auricular fibrillation and electrocardiographic abnormalities suggesting myocardial infarction. Death occurred after eight years of progressive heart failure. Microscopic studies were not described in the reports on these last two patients.[79,89] The only case[104] in which no mention was made of associated cardiovascular factors was that of a man, 45 years of age, who had cardiac failure for about four years. Nineteen months before death, this patient suffered a dissecting aneurysm just distal to the coarctation.

Despite the existence of numerous cardiovascular factors which tended to produce progressive congestive failure, some of these patients did surprisingly well. The patient with marked aortic stenosis, coronary disease, arteriolar nephrosclerosis, and an extreme coarctation had congestive failure for five years before he died at the age of 35 years.[73] A 34-year-old woman had a past history of rheumatic fever; she developed the first signs of congestive failure during her only pregnancy, was delivered of a living child by cesarian section, and died six days post partum. The autopsy showed a moderate coarctation and advanced stenosis of the mitral, aortic, and tricuspid valves.[1] Another patient was hospitalized thirty-six times during a period of twelve years because of congestive failure. He died at 68 years of age with marked aortic stenosis and insufficiency, marked coronary arteriosclerosis, diffuse myocardial fibrosis, and complete aortic atresia at the usual site.[98]

Hypertension was present in all but one patient who died from congestive failure in whom the blood pressure was recorded, and all of these patients showed left ventricular hypertrophy, the three largest hearts[43,79,84] weighing 1,140 (with great vessels), 1,200, and 1,240 grams, respectively. There was no apparent relationship between the duration of failure and the heart weight or degree of coarctation, probably because of associated cardiovascular factors. All six patients in whom the duration of failure appeared to be one year or less had advanced deformity, usually stenosis, of the aortic valve. The only death from congestive failure in a patient under 21 years of age occurred in a 13-year-old

girl who died suddenly with massive congestion.[103] Her aortic cusps showed extreme thickening and fusion, typically rheumatic; a moderate coarctation was present. A murmur was noticed four days after birth and repeated epistaxes occurred in childhood.

These studies should not be interpreted to indicate that coarctation does not cause congestive failure. Abbott[119] cited several outstanding examples of congestive failure in young persons with normal valves; these constituted approximately 3 per cent of her total series. In these patients the absence of other cardiovascular factors is not clearly indicated. It is logical to assume that moderate, extreme, or complete occlusion of the first part of the descending aorta with persistent hypertension would impose an extra burden on cardiac function. This assumption is borne out by a number of studies.[115,124,134,166] The present study merely indicates that the great majority of these patients did not die of congestive failure until some additional strain was placed on cardiac function. These patients died at an average age of 39.3 years, the range being from 13 to 67 years. The age decades during which most of these patients died were the decades during which most patients with chronic valvular heart disease, without coarctation, die.

Intracranial Lesions.—The majority of these patients died during the age period of 10 to 30 years from subarachnoid hemorrhage due to rupture of an intracranial aneurysm. There were eleven cases of death from intracranial lesions, and these cases were responsible for 10.6 per cent of all deaths in the series. The ages at the time of death ranged from 11 to 54 years, the average being 28.0 years. Three cases of cerebral embolism with bacterial endocarditis[23,40,41] were included with the endocarditis cases rather than with the intracranial group.

The brain was examined in nine of the eleven cases. Of these nine cases, a ruptured aneurysm was found in five.[14,17,45,68,92] Two additional patients, 11 years[39] and 36 years[100] of age, respectively, had subarachnoid hemorrhages but no ruptured aneurysm was found; the latter patient had one pea-sized aneurysm which had not ruptured. The remaining two cases in which the brain was examined were the two oldest patients in the group with intracranial lesions. One of these was a man, 47 years of age, who had dyspnea for eighteen months and died with symptoms of a cerebral vascular accident. Autopsy studies showed marked cerebral arteriosclerosis but no evidence of hemorrhage or infarction.[101] The other patient, a 54-year-old woman, died of cerebral embolism. She had three saccular aortic aneurysms, one in the ascending portion, one in the transverse portion which contained several friable thrombi, and one distal to the coarctation.[25] The two patients in whom the brain was not examined were both 22-year-old men; the cause of death was reported as probable intracranial hemorrhage.[11,21]

It is of interest to speculate on the lack of autopsied cases of cerebral hemorrhage due to cerebral arterial diseases other than aneurysm or bacterial arteritis. In view of the prolonged hypertension which these patients had, and the relationship between hypertension and vascular disease, a cerebral vascular accident

should be a fairly common cause of death in coarctation of the aorta, as it is in the so-called "essential hypertension" group. Undoubtedly such accidents occur, yet no instance could be found in this survey. A possible explanation is that these patients do not live long enough to die of "ordinary" cerebral hemorrhage, despite the fact that hypertension has been present many years, even at their younger ages.

In cases of ruptured aneurysms, one or more unruptured aneurysm may be present.[68] These aneurysms most commonly involve or are near some branch of the circulus arteriosùs (Willis) and generally are considered to be of congenital origin. Most frequently they occur at arterial junctions or bifurcations and have been considered the main cause of so-called "spontaneous" subarachnoid hemorrhage in young persons. Microscopic examination of unruptured aneurysms[45] showed a deficiency of medial tissue, often with little or no evidence of previous inflammation, which is consistent with the concept of a congenital origin. When rupture had occurred, medial fibrosis and atrophy and elastic splitting were seen. In one such case, the aneurysm apparently had "leaked" two years previously.[45] In an 18-year-old man who died of a dissecting aortic aneurysm, there had been a subarachnoid hemorrhage thirteen months before death. The aneurysm of the left middle cerebral artery was surrounded by fibrous tissue with evidence of old hemorrhage and showed "elastic tissue changes like those in the aorta."[27] In another patient,[79] there was a history of a cerebral vascular accident at the age of 38, twelve years before death. The brain was not examined.

As pressure dynamics probably have an important role in the actual rupture of vessels, it was interesting to find that systolic, diastolic, and pulse pressures tended to be somewhat higher in patients who died of intracranial lesions. However, this observation is difficult to evaluate because of the introduced factor of increased intracranial pressure. The same pressure elevations were not noted in patients who died of rupture of the aorta.

Another cause for aneurysmal dilation of an intracranial artery, particularly a vertebral branch, may be the tremendous collateral arterial development which is so common in coarctation. The vertebral arteries usually arise directly from the thyrocervical trunks of the subclavian arteries. Two cases of vertebral arterial aneurysms have been reported, but in neither case was there rupture of the vertebral aneurysm.[16,92] In the first of these two cases the vertebral arterial dilation was sufficient to produce pressure atrophy of the adjacent left cerebellar hemisphere, so that perhaps cerebellar pressure symptoms might be added to the list of clinical features of coarctation which are dependent on the extensive collateral arterial development.

In cases of coarctation in which death was not the result of intracranial disease, several incidental cerebral lesions were reported: marked arteriosclerosis with old hemorrhage[75] or encephalomalacia[24,32] and meningitis associated with bacterial endocarditis.[30]

CARDIAC AND AORTIC CHANGES

Left Ventricular Hypertrophy.—Hypertrophy of the left ventricle occurred in all cases, with two possible exceptions. These were in women, each of whom had a moderate coarctation. One patient,[46] 31 years of age, died of bacterial endocarditis; the heart weighed 330 grams. The other patient[50] died of an incidental cause at the age of 69 years, and the heart weighed 290 grams. It was difficult to determine to what extent the hypertrophy resulted solely from coarctation. Sixteen reports, in which heart weights and degrees of coarctation were included, indicated an absence of other cardiovascular factors which might cause hypertrophy. These patients were from 7 to 76 years of age. Their hearts weighed from 200 grams (age, 7 years) and 300 grams (age, 16½ years) to 525 grams (age, 25 years). The average weight was 416 grams in the thirteen patients over 20 years of age. No relationship was indicated between the heart weights and the degrees of coarctation in these cases. The reported gross and microscopic studies in all the cases showed no findings of unusual significance aside from the aortic changes and valvular lesions previously mentioned and congenital lesions.

Bicuspid Aortic Valves.—By far the commonest associated congenital lesion was a bicuspid aortic valve. This fact was stressed by Abbott,[119] who found an incidence of 23.5 per cent congenital bicuspid aortic valves in her series. In 50 per cent of the patients of her series with this congenital lesion, rupture of the aorta occurred. She also found that coarctation was a common congenital lesion accompanying this anomaly.[1]

The distinction between congenital and acquired bicuspid valves may be difficult at times. The criteria advanced by Lewis and Grant[145] and used by Abbott[1,119] were reviewed and extended quite recently.[141,142] Microscopic studies of bicuspid aortic valves very rarely were reported in this series of 104 cases that we are analyzing; in ten instances, the presence or absence of this anomaly was not mentioned.[2,11,13,17,24,42,49,59,64,82] Assuming that these ten patients did not have bicuspid aortic valves, there still were forty-four patients in whom descriptions indicated that bicuspid aortic valves, apparently of the congenital type, were present, an incidence of 42.3 per cent. There were three additional cases in which the bicuspid aortic valves apparently were of acquired origin.[35,54,84] This incidence is somewhat greater than that reported by Abbott.[119] The incidence of bicuspid valves was particularly high (60.9 per cent) in those patients who died of bacterial endocarditis or aortitis. On further study, the incidence of bicuspid valves in the group with bacterial aortitis (unassociated with bacterial endocarditis) was no higher than in any other group (33.3 per cent), but the incidence in the bacterial endocarditis series was significantly greater (70.6 per cent). Of seventeen patients with coarctation and associated bacterial endocarditis, fifteen had bacterial vegetations upon the aortic cusps. In eleven of the fifteen patients the cusps were congenitally bicuspid. In the other two patients with endocarditis, the mitral rather than the aortic cusps were involved.

This observation that nearly three-fourths of the patients with coarctation and bacterial endocarditis had bicuspid aortic valves raises the question whether

the presence of coarctation increases the frequency of development of bacterial infection on these valves. The incidence of bacterial endocarditis on bicuspid aortic valves not associated with other congenital cardiovascular lesions has been stated to be approximately 40 per cent,[1] while in this series the same incidence in cases of bicuspid aortic valves with coarctation was 27.3 per cent. From these data it does not seem likely that coarctation, per se, increases the incidence of bacterial endocarditis.

The main clinical importance of bicuspid valves seems to be that they are frequent sites for the development of bacterial infection. The suggestion has been made that the development of bacterial endocarditis on bicuspid valves is more dependent on previous rheumatic valvulitis than on the presence of the congenital anomaly itself.[141,142] Two patients had bacterial vegetations on mitral leaflets which appeared to have been damaged previously, while the aortic valves, one of which was bicuspid,[40] appeared to be undamaged. Also, of six patients with bacterial aortitis, five had undamaged heart valves (two of these patients had bicuspid aortic valves) and the other had marked calcific aortic stenosis. However, previous rheumatic damage does not readily explain bacterial invasion of the aorta, of a patent ductus arteriosus, or of an interventricular septal defect. Thus, the exact role of congenital bicuspid valves in the pathogenesis of superimposed bacterial endocarditis is not clear.

Recent studies[137,153] suggest that rheumatic carditis is much more frequent than is realized generally, with gross lesions often of slight extent. Descriptions of the bicuspid aortic valves in this series indicated that previous rheumatic valvulitis was more frequent than bacterial endocarditis. Of the forty-four examples of coarctation with congenital bicuspid aortic valves, the valves were involved by previous valvulitis, apparently rheumatic, in 43 per cent and by bacterial endocarditis in 27 per cent, and in 30 per cent the valves appeared grossly normal. While these findings may seem to suggest that this congenital anomaly is more vulnerable to rheumatic inflammation than are normal aortic cusps, this postulate lacks proof. It is our impression that bicuspid aortic valves commonly accompany coarctation, frequently are the site of rheumatic valvulitis, and are liable to bacterial invasion either because they are congenitally bicuspid or because they have been affected previously by rheumatic inflammation of varying extent.

Associated Rheumatic Heart Disease.—A study was made of the incidence of rheumatic heart disease in these cases. Of ninety-three instances in which fairly complete valvular descriptions were given, there were four cases of mitral stenosis, fifteen cases of "typically rheumatic" aortic or mitral valvular disease (exclusive of mitral stenosis), ten cases of "slight thickening" of aortic or mitral valves, and eleven cases of "calcific aortic stenosis," making a total of forty cases, that is, 43 per cent, with valvular disease. Although the incidence of typically rheumatic valvular disease (nineteen cases or 20.4 per cent) is increased over the same incidence (7.7 per cent) in a series of 4,437 autopsies at the Peter Bent Brigham Hospital,[162] this increase is probably more apparent than real and most likely depends on the variability of rheumatic criteria. Furthermore, mitral

stenosis, unquestionably rheumatic in genesis, was found in approximately the same frequency in this series (4.3 per cent) as in the series of 4,437 autopsies (5.1 per cent). Abbott,[118] in her study of 1,000 cases of congenital cardiac disease, found 222 cases of "acquired valvular disease." One may suspect that there is an increased incidence of associated rheumatic heart disease in this group of cases of coarctation but the evidence is not conclusive.

Other Congenital Anomalies.—These included cases suggesting some combination of adult and infantile types of constriction,[7,15,27,48,69,78,83,85,88,89,94,98,101] patent ductus arteriosus,[20,30,89] interventricular septal defects,[36,94] patent but competent foramen ovale,[51,54, and probably 42] subaortic stenosis,[80,83] anomalous origin of aortic arch vessels,[6,27,31,34,47,57,64,71] bifid coronary artery,[54] unequal width of aortic cusps,[15,80] accessory mitral cusps,[27] minor anomalous aortic cusp insertions,[91] hypoplastic descending aorta,[24,26,36,44,59,74,80,102] hypoplastic abdominal aorta,[9,21,22,41,42,89,92] hypoplastic descending and abdominal aorta,[8,17,48] considerably thickened aorta just distal to coarctation,[70] and hypoplastic ascending aorta.[91,102] There were also occasional minor anomalies affecting other parts of the body than the cardiovascular system.

Degree of Coarctation.—Following the method of Abbott,[119] these cases were classified into three degrees of stenosis, according to the size of the lumen through the coarctated area: *moderate*, 0.5 cm. or somewhat more; *extreme*, less than 0.5 cm.; and *complete*, atresia (that is, complete occlusion). In most of the extreme cases only a hair, bristle, or fine sound could be passed through the lumen. The frequencies of these types of stenosis in comparison to Abbott's (in parentheses) were as follows: moderate, 33.3 per cent (22.5 per cent); extreme, 41.5 per cent (54 per cent); and complete, 25.2 per cent (23.5 per cent). In five cases the degree of coarctation was not indicated. There was no evident relationship between the degree of coarctation and the ages or causes of death, levels of blood pressure, incidence of congestive failure, or cardiac weight. On the other hand, there was an apparent relationship between the degree of coarctation and the extent of collateral arterial development demonstrated at autopsy. In twenty-one patients in whom these collateral anastomoses were very marked, no examples of moderate coarctation were found, the degree of coarctation being equally divided between the extreme and complete groups. On the contrary, all six patients in whom no collateral circulation was demonstrable at autopsy had moderate coarctation[9,10,46,78,85,91]; the ages ranged from 8 to 31 years.

Probably because of its relationship to collateral arterial development with resultant rib erosion, the degree of coarctation appeared to be related to the incidence of ante-mortem diagnosis. In eighty-seven cases it was possible to ascertain definitely whether ante-mortem diagnosis had been made. There were forty-two cases in which the diagnosis had been made; the degree of coarctation was not stated in two. There were forty-five cases in which diagnosis was not made; the degree of coarctation was not stated in one. Of the diagnosed cases, 25 per cent had moderate and 35 per cent had complete coarctations,

while of the undiagnosed cases, 48 per cent had moderate, and but 9 per cent had complete coarctations. Ante-mortem diagnoses were made in 40 per cent of the entire series of cases, in contrast to 14 per cent in Abbott's series.

CLINICAL FEATURES

Murmurs.—The murmur in coarctation of the aorta is systolic in time and is heard over the precordial region, especially at the base, and often in the back between the scapulas or alongside the lower dorsal spine. Its intensity is moderate to extremely loud. The loudest types of murmurs are accompanied by a thrill and are widely transmitted to the neck and elsewhere. Transmission of murmurs has been shown to be dependent primarily on intensity and not on direction of blood flow.[144] However, more diagnostic of coarctation than the finding of a systolic murmur in the back is the observation that this murmur accompanies a murmur of only moderate intensity anteriorly, or, rarely, a murmur of less intensity anteriorly. For example, one may suspect coarctation if a murmur is heard between the scapulas, and yet the murmur heard anteriorly is but Grade 2 in intensity. In one case[17] the murmur in the back was described as louder than that over the precordium, and another report[24] described a murmur which was heard only posteriorly. Systolic murmurs were heard in all sixty-six cases in which mention was made of physical examination of the heart; in twenty-three of these it was stated that a murmur was heard posteriorly. We, in our limited experience, have never seen an instance in which a systolic murmur was entirely absent or was louder in the back than over the precordium.

One wonders about the mechanism of production of this systolic murmur. The fact that it is usually loudest over the precordium would rule against the possibility of the collateral channels themselves giving rise to the bruit; the finding of a systolic murmur over an enlarged intercostal or scapular artery may as well be due to murmur transmission. From analogy with the production of murmurs in chronic valvular heart disease, one reasonably could explain the systolic murmur on the basis of stenosis of the aorta, this stenosis being more distally situated than that in chronic valvular disease. In no case of complete aortic atresia in which a systolic murmur was noted was there proof that the coarctation alone produced the murmur,[13,17,48,83,86,87,95,98] since some other condition such as valvular or subaortic stenosis was present. One possible exception was the case of a 13-year-old boy who died of a ruptured intracranial aneurysm.[68] This patient had a rough precordial systolic murmur, maximal in the third left interspace. In addition to complete aortic atresia, he had a bicuspid aortic valve, one cusp of which was much larger than the other, with a large median raphe. There was also patency of the ductus arteriosus for one-half its length on the pulmonary side. A case of interest was that of a man, 50 years of age, with complete aortic atresia, who died of bacterial endocarditis of the aortic valve. This patient was reported to have had only a diastolic murmur.[90] In one patient in whom the degree of coarctation was not mentioned but in whom collateral circulation was clinically evident, the statement was made that no bruit was heard over the anterior or posterior thorax,[82] and in another case of

complete atresia[28] no bruit was reported. However, these observations do not prove that stenosis of the aorta is the only mechanism responsible for the murmur.

A diastolic murmur is not found in uncomplicated coarctation of the aorta. When present (in twenty cases in the series) it was associated with aortic valvular deformity including bacterial endocarditis, or patency of the ductus arteriosus, except in three instances, in which the valvular appearance was not described or the patient was in shock.[11,14,91]

Collateral Circulation.—The extensive collateral circulation which develops in coarctation has been thoroughly diagrammed[143] and can be well visualized by post-mortem x-ray study after injection of radiopaque material.[17,100] The degree of collateral dilation, as well as the exact routes involved, determines, to a large extent, the signs and symptoms in an individual case.

Visible pulsation, and sometimes tortuous vessels, may be present in intercostal, axillary, suprasternal, carotid, deltoid, brachial, supraclavicular, suprascapular, subscapular, interscapular, or superficial epigastric regions. Rarely, aneurysmal dilation of a vessel may be palpated.[8] In one case an aneurysm of the innominate artery was suspected.[102] Flushing, headaches, buzzing, a sensation of warmth or fullness in the head or upper extremities, a pounding sensation, nodding of the head, or epistaxis may be noted; these subjective sensations are sometimes exacerbated by bending or stooping. These symptoms, when combined with those indicating decreased arterial pressure in the lower extremities, particularly suggest coarctation.

Differences of the Circulation in the Two Upper Extremities.—Uncommonly there may be a marked difference of circulation of the two upper extremities. This usually consists of a decreased circulation in the left arm[133] because of encroachment upon the orifice of the left subclavian artery by the coarctation, which results in partial occlusion of this vessel. This extremity may then show decreased warmth and less redness, a lower blood pressure, a smaller or even absent pulse, and occasionally numbness or tingling. Variations of circulation of the two upper extremities have been discussed in some detail.[140] The opposite situation, with decreased circulation of the right arm, has been described[64] and apparently is due to a congenitally small right subclavian artery.

Results of Increased Arterial Supply to the Upper Part of the Body.—Other results of the increased arterial supply to the upper part of the body may be noted, such as relative overdevelopment of tissues (particularly in contrast to the lower extremities), full, tortuous retinal arteries,[138] enlargement of the mandibular arteries with prognathism, and relative increase in premaxillary dental pulp.[147] The possibility of symptoms from vertebral artery dilation already has been discussed in the case with unilateral cerebellar atrophy.[16] Another patient[136] showed transverse myelitis which apparently resulted from enlargement of the spinal artery. Mental aberration with repeated transient paralyses has been reported.[40] The thyroid arteries may be enlarged and one author,[89] who found that two of his patients (autopsies not reported) had symptoms of hyperthyroid-

ism with elevated basal metabolic rates (to plus 42 per cent), considered that increased blood supply might be a factor in thyroid overactivity. A few similar cases have been reported.[13,23,121,126,134,146] These reports do not establish the existence of hyperthyroidism either because there were present factors which per se might raise the metabolic rate or because no pathologic studies of the thyroid gland were made. For example, a woman, 30 years of age, had exophthalmos, throbbing neck vessels, warm hands with cold feet, tremor, and an enlarged thyroid gland. She developed alpha streptococcic bacteremia, with fever, pallor, clubbing, petechiae, a palpable spleen with infarction, and hematuria, and died of cerebral embolism from bacterial endocarditis.[23] The basal metabolic rate was not determined and the thyroid gland was not examined pathologically.

Radiologic Findings.—Radiologic demonstration of *rib erosion*, or notching of the lower borders of ribs, depends on the development of collateral arterial circulation. Since this finding was described,[75,152] ante-mortem diagnosis probably has been made most frequently by the radiologist. In only forty-three cases in this series was its presence or absence noted. Rib erosion was present in 75 per cent of these forty-three cases, only 10 per cent of which had moderate coarctations. On the other hand, 80 per cent of the cases without rib erosion had moderate coarctations. This important sign has been thought to depend somewhat on age, for it usually has not been seen until the second decade or at least the end of the first decade of life.[41] In one case in this series it was demonstrated in an 11-year-old boy.[39] Other reports indicate that rib erosion occurred at a slightly earlier age.[123,163] One instance of rib erosion demonstrated at the age of 9 months[148] suggests that further studies are indicated.

Other radiologic findings may include absence or reduction in size of the aortic knob, especially striking with hypertension which ordinarily accentuates this portion of the aorta; dilation of the ascending aorta; lack of prominence of the descending aorta; or a narrowing or defect of the descending aorta at the level of the pulmonary artery. The latter observation established an ante-mortem diagnosis of coarctation in a 31-year-old woman who had no hypertension of the upper extremities or hypotension of the lower extremities and no rib erosion.[46] This patient had precordial systolic and diastolic murmurs and a vigorous suprasternal systolic pulsation and died of bacterial endocarditis of a bicuspid aortic valve. There was a moderate coarctation. To this list of radiographic observations should be added the demonstration of cardiac hypertrophy and the visualization of the coarctation by intravascular injection of diodrast.[132,155]

Decreased Arterial Blood Pressure in the Lower Extremities.—This finding may be the first clue that coarctation exists, particularly when it is accompanied by an increased arterial circulation in the upper extremities with hypertension. Routine palpation of the femoral pulses, especially in young persons with hypertension, frequently establishes the diagnosis. The pulsations in the abdominal aorta, popliteal, tibial, or dorsalis pedis arteries, as well as the femoral, may be reduced or absent. In coarctation, the pulse in the lower extremities has been shown to occur later than in the radial arteries.[61-63,170] The blood pressure in the

lower extremities may be low or unobtainable instead of being approximately equal to, or greater than, that in the upper extremities.

In this series, symptoms due to lowering of the arterial pressure in the lower extremities included coldness, pallor, numbness, or pain in the legs, intermittent claudication, and weakness. Whenever hypotension of the lower extremities was mentioned, it was present, with the one exception previously cited[46] in which the diagnosis was made solely by the x-ray findings. All degrees of coarctation were noted. The youngest patient with decreased femoral pulsations studied post mortem was a 5-year-old girl who had a moderate coarctation and severe renal disease. The brachial arterial pressures were as high as 220/190, while the highest systolic pressure in the lower extremities was 125 mm. Hg.[88] This case illustrates that the difference between the pressures in the upper and lower extremity is probably more important than the actual pressures.

Hypertension.—Increased pressure in the upper extremities was present in almost all of the seventy-four patients in whom pressures were recorded. There were only five patients in whom an approximately normal brachial pressure was reported; insufficient data were presented in three patients.[2,58,95] One had moderate coarctation without other signs,[46] and one had auricular fibrillation.[41] Little significance can be attached to single blood pressure observations, as evidenced by a case in which the reading was 122/80 at one time and 180/85 at another time.[29] Variations between the pressures in the two arms have been discussed previously.[140]

The pathogenesis of this hypertension has been the subject of speculation.[124,125,129,130,150,157,158,164,165] Two mechanisms have been suggested. First, the increased pressure may be the proximal result of aortic occlusion, and, second, the constriction in the descending aorta may act similar to the Goldblatt clamp and produce a hemodynamic renal change. In this series, the brachial arterial pressures most commonly showed moderate elevation of the systolic level to approximately 160 to 180 mm.; the diastolic levels often did not rise above 90 millimeters. This pressure range is the type considered more typical of resistance in the larger arteries, in contrast to the higher diastolic levels with relatively narrow pulse pressures which are thought to indicate arteriolar resistance. Experimental renal hypertension generally is of the latter type and should be present in all parts of the body and not restricted to the upper extremities. Most patients showed lowering of both systolic and diastolic levels in the lower extremities; only two cases were reported in this series in which one or both pressures were higher in the lower extremities.[81,82] The whole question is complicated by the complexity of the pathogenesis of hypertension and by the fact that some cases in this series may have had renal disease of some magnitude.

Microscopic examinations of arterioles proximal and distal to coarctations, both by biopsy[131] and at autopsy,[90] have appeared to show no significant differences, although more marked sclerosis in vessels in the arterial distribution proximal to the coarctation was described in one case.[128] There were insignificant differences in mean arterial pressures in relation to the various degrees of coarctation.

Many patients had few symptoms with the long-standing hypertension. One patient had hypertension at the age of 10 years and was asymptomatic at the age of 33 years, when the blood pressure was 220/110.[164] A second report indicated a nine-year asymptomatic span though hypertension existed from the age of 12 to the age of 21 years.[121] Another patient had a normal blood pressure recorded at 15 years; at 18 years the systolic level was 180 mm., and at 23 years the pressure reached 166/106. The hypertension produced no symptoms.[161]

One feature of importance in the diagnosis of coarctation needs further investigation, and that is the earliest age at which hypertension may be found. Recently, a brachial systolic arterial pressure of 180 mm. has been observed in a 9-month-old infant with coarctation.[148] Otherwise, the earliest recorded ages at which hypertension was observed appeared to be from 3[156] to 5 years.[88,169] Even at these early ages there was left ventricular hypertrophy. One of the 5-year-old patients also had renal disease.[88]

SUMMARY AND CONCLUSIONS

A series of 104 autopsied cases of moderate, extreme, or complete degrees of the "adult" type of coarctation of the aorta in patients 2 years of age or older, which have been reported since Abbott's review in 1928, has been reviewed. As a result of this study, the following conclusions are presented:

1. Although coarctation occasionally was compatible with long life, at least 61 per cent of the patients died before or during their fortieth year of life, the average age at death being 35.0 years. The lesion was more common in males.

2. The causes of death and their frequencies were as follows: incidental causes, 26 per cent; rupture of the aorta (most commonly the ascending portion), 23 per cent; bacterial endocarditis or aortitis, 22 per cent; congestive failure, 18 per cent; and intracranial lesion (exclusive of embolism from bacterial endocarditis), 11 per cent.

3. Rupture of the aorta or an intracranial lesion accounted for one-third of all deaths. These accidents occurred mainly in the second and third decades of life. The commonest cause of an intracranial lesion was rupture of an arterial aneurysm, probably congenital, which produced subarachnoid hemorrhage. Survival rarely occurred after either type of rupture.

4. Bacterial endocarditis or aortitis occurred throughout the first five decades of life, most commonly was due to alpha streptococci, and most often (61 per cent) was associated with a bicuspid aortic valve, apparently congenital. Bacterial aortitis was found just distal to the coarctation or in the ascending aorta.

5. Congestive failure was common, but almost all patients who died of this cause had evidence of additional cardiovascular burdens, chiefly marked chronic valvular disease. Despite such handicaps, these patients sometimes lived for surprisingly long periods. Their ages at death corresponded to the ages at death of patients dying from valvular disease with congestive failure.

6. Bicuspid aortic valves were by far the commonest congenital anomaly associated with coarctation. This anomaly was present in 42 per cent of the

cases in this series, particularly in cases with bacterial endocarditis (71 per cent). They frequently appeared to have been the site of previous rheumatic inflammation.

7. Cardiac hypertrophy was the rule. Dilation of the aorta was very common, especially in the ascending aorta, and occasionally proximal or distal to the coarctation.

8. The degree of coarctation appeared to be related to the extent of collateral arterial development and the frequency of ante-mortem diagnosis, which was 40 per cent in this series, in contrast to 14 per cent in Abbott's series. The various signs and symptoms which apparently depend on this collateral circulation are discussed.

9. A systolic murmur of moderate intensity (Grade 2 to 3) occurs in coarctation. It is present characteristically over the upper precordium and in the left interscapular region and is generally almost as loud in the back as anteriorly. Certain observations are presented which suggest that this systolic murmur is due mainly to stenosis of the aorta at the site of the coarctation. A diastolic murmur was not noted in uncomplicated coarctation; when present, it indicated an additional aortic, or less commonly, mitral, lesion, or associated patency of the ductus arteriosus.

10. The cardinal features of coarctation include (a) *hypertension* of the upper extremities (frequently not marked), (b) *lower blood pressure* of the legs (such as absent femoral pulses), (c) *collateral arterial anastomoses* (with *rib erosion* by x-ray), (d) the *systolic murmur* (which may be noted shortly after birth), and (e) *cardiac hypertrophy*.

11. Coarctation of the aorta, although not common, should be diagnosed as early as possible, for it is likely that surgery would be more feasible at that time than later when the aortic wall has become thinned and dilated. When resection of the area of coarctation with anastomosis of the cut ends of the aorta is not feasible, surgical treatment of the associated hypertension may be of value in certain cases, perhaps in patients beyond 15 to 20 years of age. This procedure has been performed in a small series of patients to date.[168] The use of artificial vascular channels may increase the number of future cures of coarctation. The frequent finding in this study of congenital intracranial aneurysms and bicuspid aortic valves, both of which lead to fatal complications, militates somewhat against the otherwise hopeful expectations from surgery. On the other hand, surgery affords the only possible cure of this condition.

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THE TREATMENT OF SHOCK ACCOMPANYING MYOCARDIAL INFARCTION

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THE shock picture in acute myocardial infarction has been a recognized clinical entity since Herrick's[1] classic description in 1912. Experimentally however, occlusion of coronary arteries has failed to produce the frank vascular collapse seen so often clinically. Von Bezold,[2] in 1867, reported a sharp fall in arterial blood pressue in rabbits after compression of the coronary vessels and several years later Michaelis[3] noted comparable changes. In 1930, Sutton and Lueth[4] observed an immediate drop of 30 to 50 mm. of mercury in the arterial pressure of dogs after partial coronary compression. Condorelli[5] made similar observations following coronary ligation. Feil, Katz, Moore, and Scott,[6] on the other hand, found little or no significant change except where an additional factor such as some arrhythmia supervened. Lowe[7] injected phenol into the myocardium and found that even extensive myocardial damage so produced caused no change in the blood pressure. Gross, Mendlowitz, and Schauer[8-11] have recently investigated the problem under a variety of conditions and have concluded that there is no immediate fall in blood pressure following coronary ligation, but they report a drop which becomes conspicuous after twenty-four hours and persists for about one week. The diminution in cardiac output occurring immediately after ligation is thought to be accompanied by a compensatory peripheral vasoconstriction which serves to maintain the blood pressure temporarily. At the end of twenty-four hours the vasoconstruction decreases, thus permitting hypotension to develop.

Clinically, a different situation prevails. The high incidence of shock or a shocklike state following coronary thrombosis is generally acknowledged. Master, Dack, and Jaffe[12] found, in a series of 135 cases of coronary thrombosis, that manifestations of shock were present in approximately 50 per cent. These manifestations included a precipitous fall in blood pressure, collapse, cold extremities, moist, clammy skin, grayish pallor, and unconsciousness. There is disagreement as to whether these clinical findings represent a true peripheral vascular collapse or the sudden development of cardiac insufficiency. Certainly the described shock picture is in marked contrast to the dyspnea, pulmonary congestion, venous engorgment, and edema found in congestive failure.

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Harrison[13] has pointed out that a shock picture resembling peripheral vascular collapse may occur in "acute forward heart failure." This is ascribed to a decrease in blood supply to the tissues, resulting from the inability of the heart to maintain its normal output. Fishberg[14] and Stead and Ebert[15] maintain that this is the responsible mechanism following myocardial infarction and have applied to it the term "cardiac shock"; however, as Harrison has noted, in "acute forward failure" due to the tachycardias, Adams-Stokes syncope, etc., the peripheral veins are usually distended, while following infarction they are generally collapsed. Harrison[13] and Master and his associates[12] suggest as an explanation of this critically important difference that a reflex nervous mechanism initiated by infarction induces peripheral collapse. The work of Condorelli,[5] Michaelis,[3] and Sutton and Lueth,[4] who found that the drop in blood pressure following coronary ligation could be prevented by previous denervation of the heart, tends to substantiate this view.

Diminished venous return to the heart occurs invariably in all forms of peripheral circulatory failure. This concept, originally introduced and supported by the work of Henderson,[16] has been said by Wiggers[17] to be "the keystone of all modern conceptions of shock." It therefore becomes important to evaluate the shock picture in coronary thrombosis in terms of this concept. The studies of Fishberg, Hitzig, and King[18] on a series of fifty-nine cases of coronary thrombosis indicated that the development of shock was usually associated with a marked decrease in venous return to the heart. In these patients there was generally a diminution in circulating blood volume, the venous pressure was lower than normal, and there was no significant increase in the circulation time through the lungs. It thus becomes difficult to place the collapse associated with myocardial infarction in any other category than that of shock. This can be described, according to Atchley,[19,20] as "medical shock" and is therefore akin to the circulatory collapse observed in such conditions as diabetic coma, pneumonia, and typhoid fever. This entity is distinct from that encountered in congestive heart failure. It is not paradoxical, however, to note that even in the presence of severe peripheral collapse, evidence of venous and pulmonary engorgement may appear. The myocardial damage may so reduce cardiac efficiency that the classic picture of congestive failure can develop and be superimposed on the shock. This is particularly likely to occur in the presence of pre-existing cardiac damage.[12] The height of the venous pressure will depend, therefore, on whether myocardial failure or shock predominates.

The prognosis of the patient with coronary thrombosis in shock is ominous. Master and co-workers,[21] Fishberg,[22] and Levine[23] state that a systolic pressure of 80 mm. or less is generally of very grave significance. Although recoveries take place, they are uncommon.[24]

Wiggers[17] has shown in experimental hemorrhagic shock that if mean arterial pressures of from 35 to 80 mm. are allowed to persist for more than a few minutes or several hours, depending upon the severity of the hypotension, a further abrupt drop occurs and death results despite replacement of the blood. This indicates that the persistence of such low blood pressures will usually precipitate

irreversible shock. It is not entirely clear what these precipitating mechanisms are, but failure of both the heart and the vasomotor center appear to be implicated. In the problem under consideration the former is of special interest. There is some evidence that during shock the myocardium is depressed.[17] Wiggers[17] believes that myocardial depression may be assumed a priori in prolonged hypotension, since there is obviously a significant decrease in coronary blood flow. It seems likely, therefore, that in the presence of a myocardial infarction prolonged hypotension resulting in additional myocardial anoxia is of particularly serious import.

Specific antishock therapy in coronary thrombosis is generally not mentioned in the literature or mentioned only to be discouraged.[25-27] Most authors feel that the use of plasma and blood is contraindicated in the presence of myocardial injury. Gilbert[28] states that in shock following infarction, "Blood pressure should be left where it is and not tampered with," and Stroud[29] suggests that "perhaps a drop in blood pressure is an effort on the body's part to protect the myocardium." The very high mortality among such patients in shock militates against this viewpoint. Although cardiac failure is ever imminent and even rather frequent[12] in those surviving for any appreciable length of time, it would appear that treatment of the shock might be indicated in the absence of evident signs of failure and that the problem of cardiac failure should be made a matter of concern only after the critical shock period is safely past. Levine,[30] in the most recent edition of his textbook, mentions a patient with coronary thrombosis in profound collapse who was given an infusion of 250 c.c. of plasma which was repeated four hours later with great benefit.

An unusual combination of clinical conditions led to the use of vigorous antishock therapy in a patient with coronary thrombosis, with apparently excellent results.

CASE REPORT

The patient was a 65-year-old male singer admitted to Billings Hospital on Jan. 30, 1946, complaining of exertional dyspnea for fifteen years, orthopnea and swollen legs for two months, and a productive cough for one week. For twenty-five years he had been treated intermittently for duodenal ulcer which responded to dietary management and alkalies. Six months before admission roentgen examination revealed complete healing of the ulcer. Recurrent attacks of back pain had been explained on the basis of x-ray evidence of osteoarthritis of the thoracic spine.

Physical Examination.—The patient was dyspneic, orthopneic, and mildly cyanotic. The fundi showed increased tortuosity of the vessels and arteriovenous nicking. A few fine, moist râles were present at both lung bases. The apex impulse was palpated in the sixth intercostal space 11 cm. from the midsternal line. There were no thrills. The heart sounds were regular and of fairly good quality; A_2 was greater than P_2. A blowing systolic murmur of moderate intensity was heard over the entire precordium. The blood pressure was 180/108. Pulse rate was 104 per minute. The liver edge was palpable 5 cm. below the right costal margin. There was pitting edema of both lower extremities.

Laboratory Examination.—The hemoglobin was 14 Gm. per 100 c.c.; the red blood cells, 4.8 million per cubic millimeter; and the white blood cells, 13,100 per cubic millimeter. The differential count was normal. The urine was negative except for 200 white blood cells per high-power field in a centrifuged specimen.

X-ray examination showed a heart that was 33 per cent oversized with a hypertensive configuration. There was mild chronic passive congestion of the lungs. Osteoarthritis of the thoracic and lumbar vertebrae was also present.

Hospital Course.—On standard therapy, including digitalization, the patient improved rapidly. One week after admission he passed a stool containing dark red blood. The hemoglobin at this time was 12.8 Gm. per 100 cubic centimeters. Five hundred cubic centimeters of whole blood were given slowly the following day. During this episode the patient developed symptoms of duodenal obstruction and was placed on dietary management. All symptoms abated within one week. Gastrointestinal x-rays showed a duodenal ulcer with a moderate degree of obstruction. At this time there was no evidence of heart failure: the dyspnea, orthopnea, râles, and edema had disappeared. Four weeks after admission the patient complained of rather severe pain in the upper back similar to the pains ascribed to arthritis on previous occasions. This was unrelieved by aspirin and codeine. Physical examination was unchanged. During the following six hours the pain became progressively more severe and spread to the left anterior chest. The patient then arose from bed, vomited a small quantity of bile-stained gastric contents, and fell to the floor.

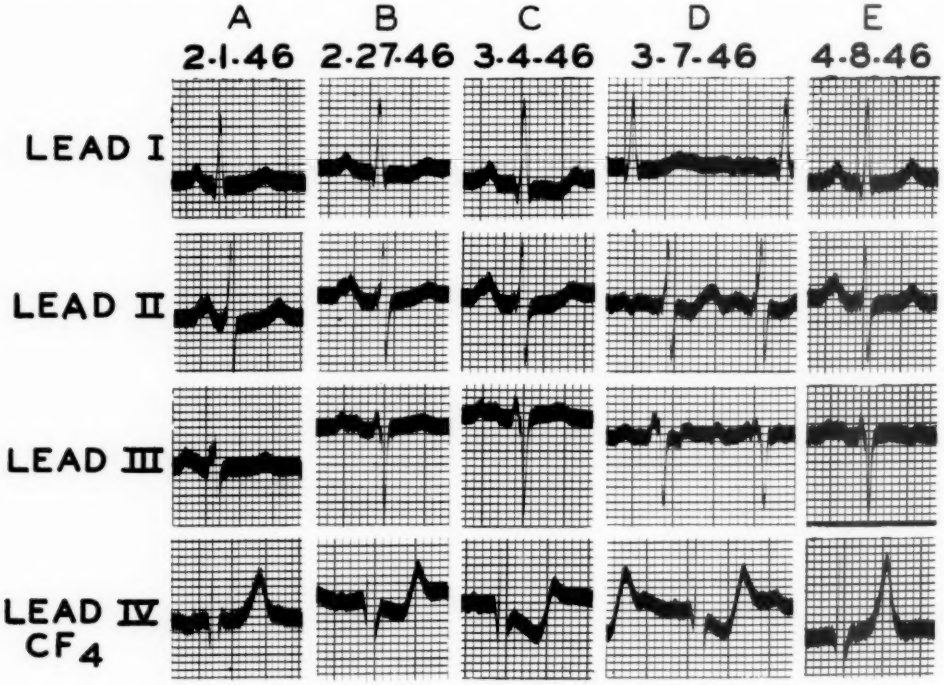

Fig. 1.—Serial electrocardiograms taken on patient B. W. *A*, On admission to the hospital suffering from heart failure. *B*, The day following onset of coronary thrombosis. *C*, *D*, and *E*, Subsequent tracings showing the development of the infarction pattern.

On examination he was semicomatose, cold, clammy, and cyanotic. Respirations were rapid and shallow. The pulse was imperceptible and no heart tones could be heard. All visible veins were collapsed. Blood pressure was unobtainable. The abdomen was soft. Rectal examination was normal. Although the patient's condition could have been attributed to either coronary occlusion or concealed gastrointestinal hemorrhage, the history of severe pain in the chest and back favored the diagnosis of myocardial infarction. Because the patient appeared moribund, vigorous treatment for shock was instituted. He was placed in the Trendelenberg position and needles

were inserted with difficulty into two of the collapsed peripheral veins. During the next forty minutes, 1,800 c.c. of plasma and 400 c.c. of whole blood were administered. The blood pressure, which had been unobtainable during this time, suddenly rose to 140/105. Plasma and blood were immediately discontinued, and the patient was closely observed for signs and symptoms of congestive heart failure. No dyspnea, râles, or edema developed subsequently. Stools were persistently negative for occult blood. The temperature, white blood count, and sedimentation rate were elevated. Serial electrocardiograms confirmed the diagnosis of myocardial infarction (Fig. 1). Ten days after the thrombosis, auricular fibrillation developed, but the rhythm later reverted to normal. The blood pressure during the postinfarction period ranged from 100/60 to 120/70. The patient was discharged in good condition on the seventieth hospital day, six weeks after the infarction.

DISCUSSION

It appears that massive transfusions were a lifesaving measure in this patient. The absence of congestive heart failure during the postinfarction period is quite noteworthy since only four weeks previously cardiac decompensation had been a prominent finding.

If the sudden collapse of this patient was the result of "acute forward heart failure," then the heart was already incapable of handling the circulatory load, and it would seem that the additional strain of 2,200 c.c. of blood and plasma intravenously should have hastened a fatal outcome. That, instead, he made a rapid and uneventful recovery would support the view that the failure was peripheral in nature and that restoration of the effective blood volume was the significant factor in his survival. The foregoing facts suggest that in cases of myocardial infarction and shock without heart failure, it may be advantageous to treat this critical complication actively. It must be anticipated that cardiac decompensation will develop in some patients following such therapy, but it should be emphasized that this occurs in many cases without such treatment. If the peripheral circulatory collapse is not corrected, it appears probable that many patients will succumb immediately. With intravenous blood and plasma there may well be an appreciable number who will recover.

Immediate venesection after return of blood pressure from shock levels may be indicated in instances where congestive heart failure follows upon the increase in blood volume and the return of pooled blood to the effective circulation. The use of digitalis, diuretics, fluid restriction, and other measures should further aid the recovery of such patients, who might otherwise die in the acute shock phase.

SUMMARY AND CONCLUSIONS

A patient with profound peripheral vascular collapse accompanying myocardial infarction received 2,200 c.c. of blood and plasma within a period of forty minutes. Recovery was rapid and uneventful. Signs or symptoms of congestive heart failure did not develop.

It is suggested that serious consideration be given to the use of blood and plasma in the treatment of shock accompanying myocardial infarction.

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A RELATION BETWEEN THE SIZE OF THE HEART AND THE VELOCITY OF THE BLOOD

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DETERMINATION of blood velocity is a simple, inexpensive procedure which enjoys wide clinical popularity. David and Bouvrain,[1] in 1940, first reported on the relation of blood velocity to heart size, although Nylin reports he had begun work along this line in 1933.[2] Nylin and Malmström made their first report on this topic in 1941.[3] One of us[4] followed David and Bouvrain's suggestion and developed a relation between the size of the heart and the circulation time. We had not had access to Nylin's earlier publication at that time. The present report amplifies and modifies our previous finding.

METHODS

Patients were selected who were known to have heart disease. Many had been or were in various stages of congestive heart failure. Blood velocity was determined with Decholin† by the method of Winternitz, Deutsch, and Brüll.[5] Each determination was made in duplicate. After an initial rest period in the supine position of fifteen minutes or more, 5.0 ml. of a 20 per cent solution of sodium dehydrocholate was injected into the antecubital vein. Three to five minutes elapsed between the first and second injection of the material. Other investigators have shown that there is little, if any, significant difference between the blood velocity determined thus and the velocity in patients who are in the basal state.[6] Most of the determinations checked within a few seconds, although on one or two occasions gross discrepancies were noted which we interpreted as mistakes on the part of the patients. These errors were not included in the tabulations. A few patients experienced disagreeable reactions, none of which were of a serious nature. No cases other than the errors noted were excluded from the tabulations. In general, checks between the first and the second estimate were less good in patients with auricular fibrillation than in patients with a normal sinus rhythm.

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†Decholin was supplied through the courtesy of Mr. Paul de Haen of the firm of Riedel-de Haen, Inc., 105 Hudson St., New York City.

Teleroentgenograms were obtained in the routine manner near the time of the determination of blood velocity. The transverse diameter of the heart was taken as the sum of the distances from the midline to the outermost border of the heart to the right and to the left. The internal diameter of the chest was measured at the level of the fourth costochondral junction rather than the customary measurement lower in the rib skirt.

RESULTS

Forty-one cases are reported. The findings are summarized in Table I. The formulation of the relationship between heart size and blood velocity reported earlier by one of us[4] is found in this larger number of cases still to be statistically highly significant (Fig. 1). Heart size was expressed as the ratio of

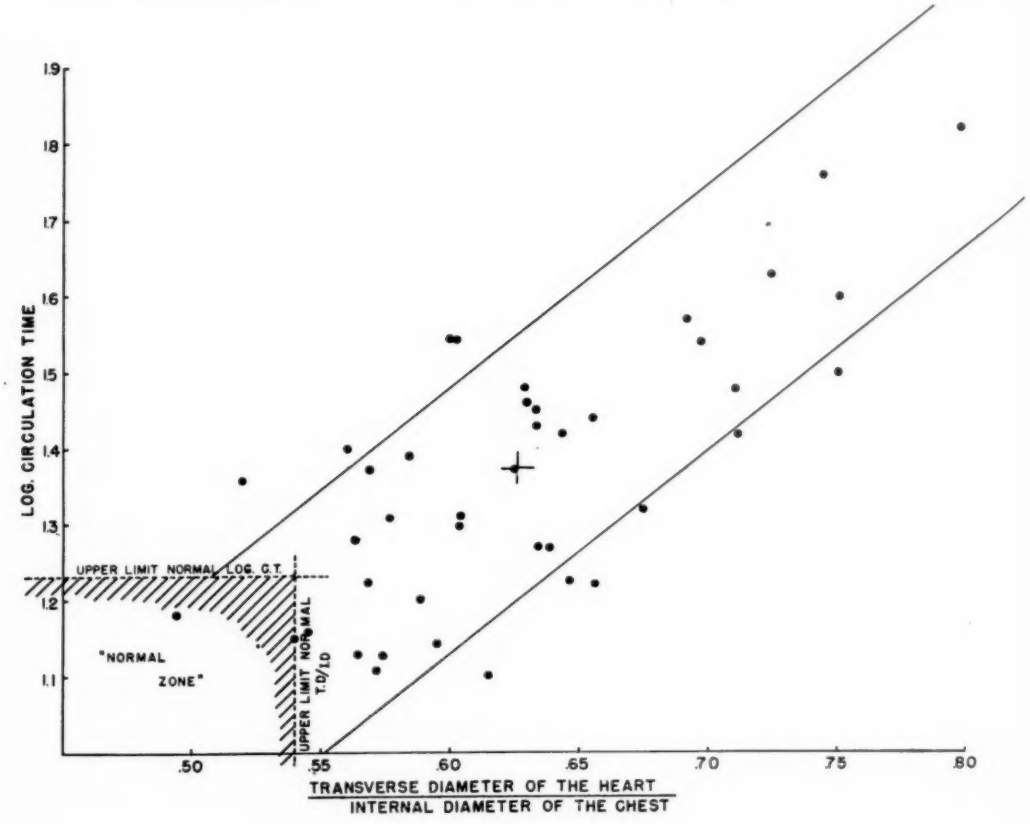

Fig. 1.—Relation of heart size $\left\{\frac{\text{Total diameter}}{\text{Intrathoracic diameter}}\right\}$ and log. circulation time.

the transverse diameter of the heart to the internal diameter of the chest (TD/ID). This ratio was utilized rather than absolute heart size because it tends to reduce to a common denominator variation due to stature and habitus. Blood velocity

TABLE I. BLOOD VELOCITY FROM ARM TO TONGUE, RATIO OF TRANSVERSE DIAMETER OF THE HEART TO THE INTERNAL DIAMETER OF THE CHEST, AND THE CUBE OF THE RATIO OF THE TRANSVERSE DIAMETER OF THE HEART TO THE INTERNAL DIAMETER OF THE CHEST IN FORTY-ONE PATIENTS WITH KNOWN HEART DISEASE

CASE	CIRCULATION TIME (SEC.)	TRANSVERSE DIAMETER OF HEART/ INTERNAL DIAMETER OF CHEST	(TRANSVERSE DIAMETER OF HEART/ INTERNAL DIAMETER OF CHEST)^3
34	12.5	.615	.233
19	13.0	.572	.187
15	13.5	.564	.179
29	13.5	.574	.189
32	13.7	.595	.211
24	14.0	.540	.157
25	14.5	.545	.162
22	15.0	.494	.120
31	16.0	.588	.203
39	16.5	.656	.282
27	16.5	.568	.183
12	17.0	.647	.271
37	18.5	.634	.255
38	18.5	.637	.258
26	19.0	.563	.178
9	20.0	.604	.220
14	20.0	.604	.220
23	20.3	.526	.146
11	21.0	.673	.305
8	23.0	.518	.139
35	23.2	.625	.244
28	23.5	.568	.183
30	24.5	.584	.199
7	25.0	.560	.176
4	26.0	.643	.266
41	26.5	.711	.359
36	26.7	.633	.254
13	27.5	.655	.281
5	29.0	.632	.252
10	29.0	.630	.250
1	30.0	.629	.249
40	30.0	.710	.358
17	32.0	.750	.422
16	34.3	.696	.337
33	34.5	.602	.218
6	35.0	.600	.216
20	36.8	.692	.331
21	40.0	.750	.422
2	43.0	.723	.378
18	57.0	.744	.412
3	66.5	.796	.505
Mean	25.268	.626	.254
Standard deviation	±11.47	±.065	±.078

was first expressed as arm-to-tongue time in seconds. When these two data for each case were plotted with rectilinear coordinates, two things were immediately apparent. First, there was significant correlation and, second, a linear plot was only a first approximation. Several functions were tried, but the most linear relationship was between the logarithm of the circulation time and the TD/ID

ratio. It was evident then, as it is now, that this empirical formulation has no physiologic rationale. It was offered as an observation without an explanation. ". . . . a correlation . . . . means nothing except statistical association between the variables, no matter how glamorous or seductive the suggestion as to casual relation may be."[7]

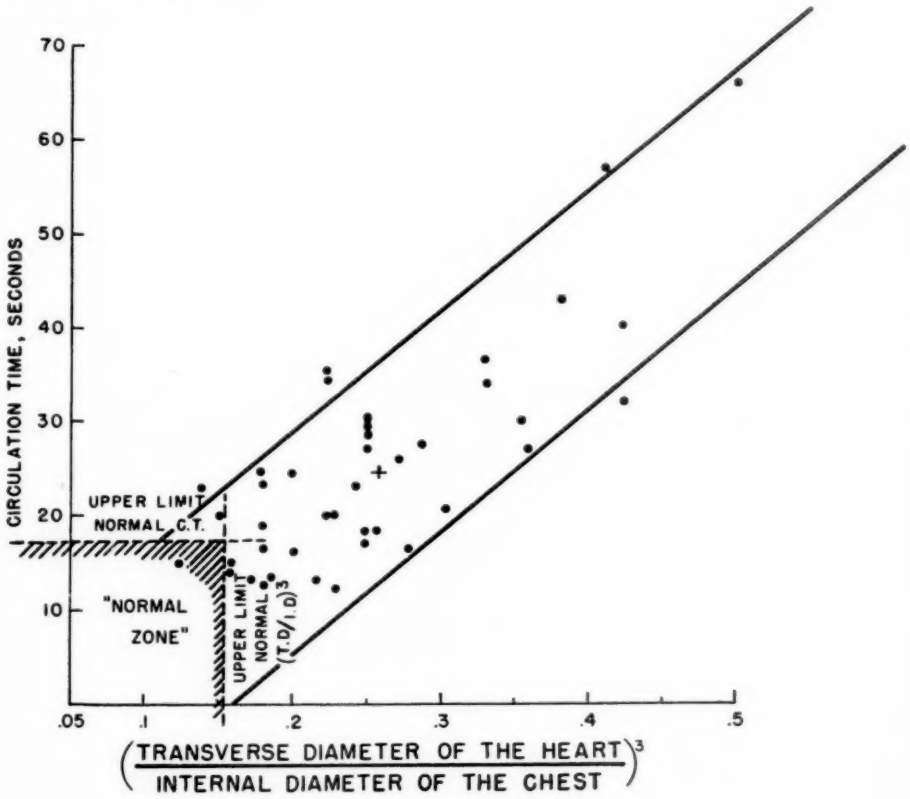

Fig. 2.—Relation of heart volume $\left(\frac{\text{Total diameter}}{\text{intrathoracic diameter}}\right)^3$ and circulation time.

The larger volume of data here reported made it possible to examine other associative relationships more critically, and we have found one such relationship which probably has real physiologic significance. The TD/ID ratio is a linear measure of the heart. The cube of this ratio is a measure of heart volume. When this volume function is plotted against observed circulation time, a highly significant correlation is found (Fig. 2). The coefficient of correlation is +0.86 with a standard error of ±0.16. Parallel lines are drawn at plus and minus one standard deviation about the axis of the respective means. These include about 88 per cent of the cases. Seventeen seconds was taken as the "upper limit of normal" for circulation time and 0.54 as the "upper limit of normal" for the TD/ID ratio measured in the manner described. Therefore, the upper limit of normal for $(TD/ID)^3$ is 0.15.

DISCUSSION

It is obvious that some relation might exist between the transverse diameter of the heart and the velocity of blood flow. In general, patients who have severe heart disease have enlarged hearts and the same group tend to have prolonged circulation times. Yet, scrutiny of similar patients with respect to certain other measurements, for example, elevated blood volume and elevated venous pressure, has not revealed any simple relation. It is generally true that a group of patients with high venous pressure will also, as a group, have high blood volumes,[8] but a direct simple correlation does not exist within a group of patients in heart failure.[4] This latter finding has been confirmed and some of the reasons for the lack of such a simple relation clarified.[9] It is, therefore, interesting that relations of heart size to blood velocity can be shown to exist.

We chose the transverse diameter of the heart and the internal diameter of the chest as more readily available than such measures as frontal area or height-weight formulas. We agree with others[10] that measurements of frontal cardiac areas in the teleroentgenogram are not reliable because the examiner has to draw most of the perimeter of the area he will measure. The transverse diameter of the heart is certainly one of the simplest and most reliable measures in common use,[10] but one needs to be critical in employing it to avoid misleading silhouettes.[11]

Selection of the level of the fourth costochondral junction for measurement of the internal diameter was based upon a suggestion to one of us some years ago by Dr. George Ramsey which, so far as we are aware, has not been published. Experience on our part has served to confirm his recommendation. At this level the chest is less subject to irrelevant variation than lower in the rib skirt. The value of securing the information desired from the film alone rather than from weighing and measuring the patient in addition is apparent. In our experience 0.54 is the upper limit of normal for the ratio between the transverse diameter of the heart and the internal diameter of the chest measured in this way.

Experiences to be published elsewhere have convinced us that, of the common methods of evaluating the circulation in cardiac impairment, the blood velocity is one of the least labile measures. It reflects the actual condition of the circulation much better, for example, than the venous pressure which is well known to fluctuate through any given day. On the other hand, the heart is only one of the numerous factors affecting the velocity of the blood. The peripheral circulation is certainly equally important, as is most strikingly seen in hyperthyroidism with heart failure. It is not the aim of this paper to advocate the determination of the velocity of the blood as more than one part of the study of impaired circulation but rather to demonstrate the simple relation which exists here within such a group of patients. This suggests that further exploration of the relation should give valuable new information about the circulation in impairment.

Over the past few years, Nylin has developed his concept of blood velocity as a function of the residual volume of the heart. At the time of the earlier work by one of us mentioned previously,[4] we had not had access to Nylin's formulation. He had stated, "There appears to be a definite correlation between the

circulation time and the size of the heart in compensated cases of cardiovascular disease."[3] More recently he has further explored this relationship[2,12] and concluded that, "The prolongation of the circulation time . . . . is not only an expression of the degree of stasis but also of the dilatation of the heart and thus of the residual blood in the heart."

In cardiac patients there is little doubt that Nylin's observations on the prolongation of the *duration* of the taste sensation[2] and the flattening of the arterial red cell dilution curve[12] are due in part to the increased amount of blood that injected material must mix with, in the heart among other places. Yet, there appears little reason to suppose residual blood in the heart could of itself slow the circulation and *substantially* delay the arrival of the *first portion* of the material at the sensitive organ by this mixing effect. The fundamental defect in congestive heart failure in all its stages is impaired *myocardial* function. The "law of the heart"[13] is no longer obeyed and work is disproportionate to heart volume.[14,15] "Residual blood in the heart" is only a secondary effect of cardiac dilatation, while cardiac dilatation is a primary effect of impaired myocardial function. It appears more logical to relate slowing of the circulation to the latter than to the former. The findings embodied in this report are in accord with Nylin's earlier formulation quoted in the foregoing.[3] We are not inclined to accept a casual relation between prolongation of the circulation time and "residual blood in the heart" per se.

Since all these patients had known heart disease, a point of practical clinical interest is that eleven patients (27 per cent) were within "normal limits" of circulation time, while only three (7 per cent) were within "normal limits" of the TD/ID ratio. This suggests the roentgenographic measurement detects cardiac abnormality with greater accuracy than the blood velocity determination. Further, only one of the group (2.5 per cent) had both a normal TD/ID ratio and a normal blood velocity which suggests that both data together form an even better clinical criterion of cardiac abnormality.

SUMMARY

1. The correlation between heart size and circulation time reported earlier by one of us[4] is confirmed as a statistical association, but it lacks an adequate rationale.

2. A highly significant correlation between a measure of heart volume and the arm-to-tongue circulation time in forty-one patients with known heart disease is described. This relationship is understandable in the light of current concepts of myocardial failure.

3. It is concluded that circulation time is proportional to relative heart volume in patients with heart disease, confirming the earlier formulation of Nylin.[3]

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ORIGIN OF LEFT CORONARY ARTERY FROM PULMONARY ARTERY

Review of the Literature and Report of Two Cases

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THE origin of the left coronary artery from the pulmonary artery has intrigued clinicians and pathologists since the anomaly was first described in 1911.[1] A total of twenty-five cases, eighteen infants and seven adults, has been reported in which this was the only cardiac abnormality.

This lesion is rare, having been found in only one out of 6,800 consecutive autopsies at the Massachusetts General Hospital.[2] The two cases described herewith were encountered in the course of 7,800 consecutive autopsies at the Mount Sinai Hospital.

These cases have stimulated continuing interest because they furnish an opportunity to study changes in the heart when the left coronary artery is perfused in vivo with partially oxygenated blood at reduced pressure.

CASE REPORTS

Case 1.—A 3-month-old white male infant was admitted to the Mount Sinai Hospital with a history of nonproductive cough and wheezing for one week. Pregnancy and delivery had been normal, and the infant weighed 8 pounds at birth. Weight gain had been satisfactory. One week before admission he developed a dry cough and fever. Examination at the pediatric clinic was negative except for some wheezing. Four days before admission, he was found to be improved. The night before admission the infant became feverish and dyspneic and coughed frequently.

Physical examination revealed a thin, pale, cyanotic, extremely dyspneic infant, with an anxious expression, who was perspiring profusely. Temperature was 102.8° Fahrenheit. Respirations were 100 per minute. The trachea was shifted slightly to the left and the left chest was somewhat retracted. There was flatness and bronchial breathing over the left upper lobe area; râles were heard at the left base, and occasional wheezes were heard throughout both lungs. The heart sounds were of fair quality, the heart rate was 200 per minute with regular rhythm, and there was a short blowing systolic murmur at the apex. The liver edge was felt two fingerbreadths below the costal margin.

X-ray examination on admission (Fig. 1) revealed enlargement of the heart to the left and a dense homogenous shadow in the left lower lung field. White blood cells were 7,900 per cubic millimeter.

On admission, the infant was considered to have pneumonia superimposed on congestive heart failure due to congenital heart disease. He was placed in an oxygen cubicle and given 3,000 units of penicillin every three hours and 0.25 Gm. sulfadiazine every four hours. He was

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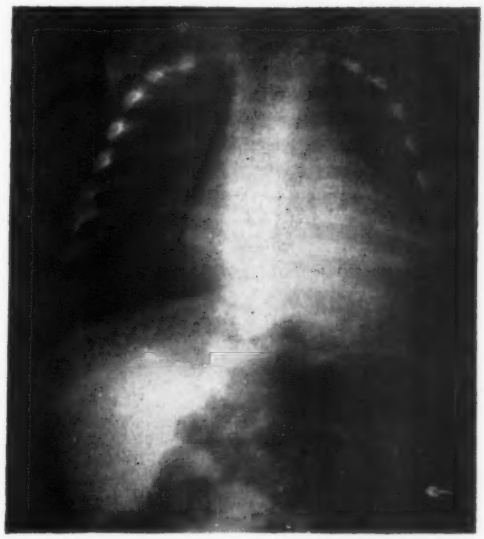
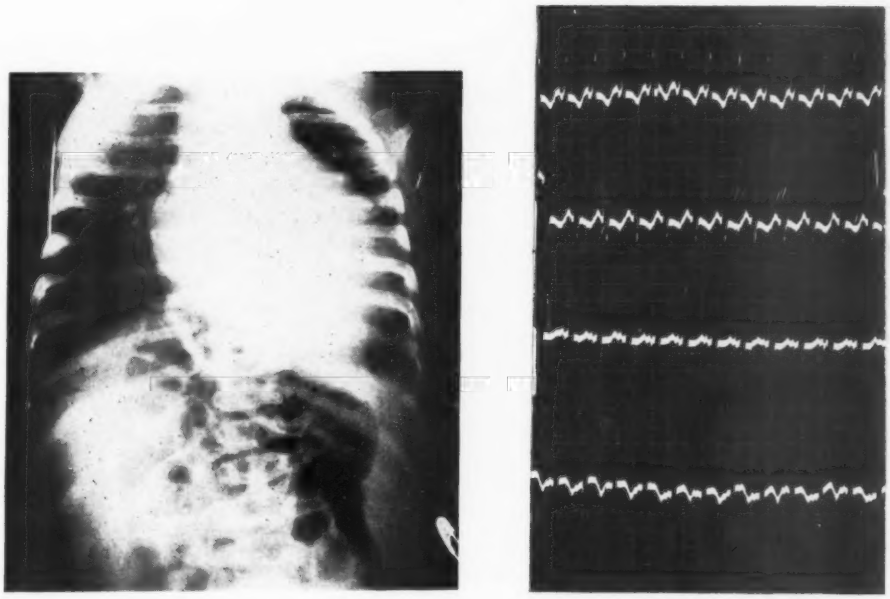


Fig. 1.—Case 1. X-ray of chest taken on admission. Enlargement of heart to left, with accentuation of pulmonary vascular markings.



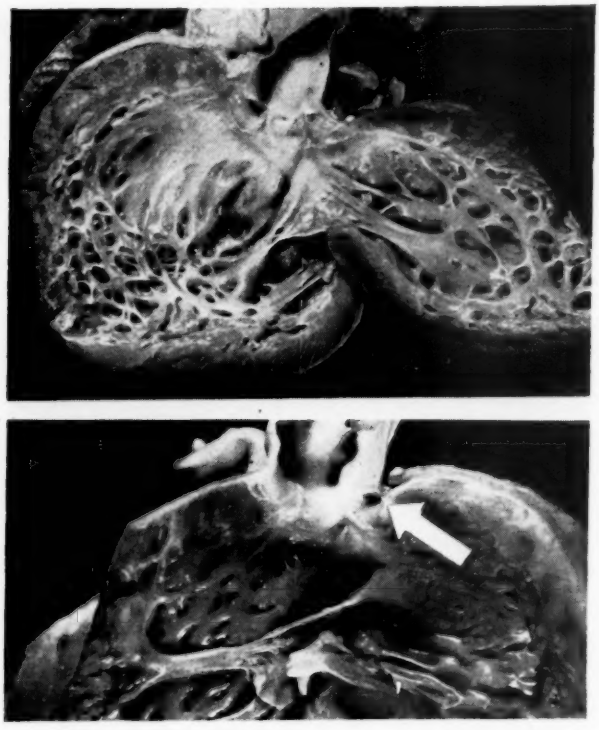
A. *B.*

Fig. 2.—Case 2. *A*, X-ray of chest taken on admission. Enlargement of heart to left, with accentuation of pulmonary vascular markings. *B*, Electrocardiogram taken on admission. No digitalis had been administered. Rate, 180. Tendency to left axis deviation. Slight depression of RST_1 and RST_2; inverted T_1 and T_2; biphasic T_4.

rapidly digitalized. The temperature gradually rose, and twelve hours after admission it had reached 105.8° Fahrenheit. There was no improvement in the dyspnea, and the infant died thirteen hours after admission.

Autopsy.—Autopsy* was performed eight hours after death. The findings were as follows: The heart weighed 102 grams (average normal, 27 grams). There was no free pericardial fluid

B.



A.

Fig. 3.—Case 1. *A*, Right ventricle. Arrow points to ostium of left coronary artery in left sinus of Valsalva of pulmonary artery. *B*, Left ventricle. Hypertrophy and dilatation, endocardial fibrosis, atrophy of anterior papillary muscle. Note absence of vascular opening in left sinus of Valsalva of aorta.

and the pericardial surfaces were smooth and glistening. There was a bluish discoloration over the epicardial surface of the left ventricle due to a very fine vascular network over an area 2 cm. in diameter. The heart was markedly enlarged. It was globular in shape because of bulging and rounding of the left ventricle and measured 7 cm. in its greatest diameter. The right auricle and tricuspid valve were normal; the latter measured 5 cm. in circumference. The right ventricle was slightly dilated and hypertrophied and measured 3 mm. in average thickness. Section of the right ventricle revealed normal-appearing myocardium. The pulmonic valve was normal; it measured 3.2 cm. in circumference. Just above the free edge was a vascular opening in the left sinus of Valsalva, which was the ostium of the left coronary artery (Fig. 3, *A*). This artery

*By Dr. L. Strauss.

branched soon after its origin and had a normal course and distribution; the vessel wall appeared normal. The pulmonary artery itself was not remarkable, and the ductus arteriosus was closed. The left atrium was slightly dilated and hypertrophied and the endocardium moderately thickened and gray. The mitral valve was normal; its circumference was 4.8 centimeters. The left ventricle (Fig. 3, *B*) was markedly dilated and bulged in a thinned area near the apex. The trabeculae were flattened, and the endocardium was extremely thickened, gray, and lusterless. The anterior papillary muscle was markedly atrophied and appeared as a gray fibrous band;

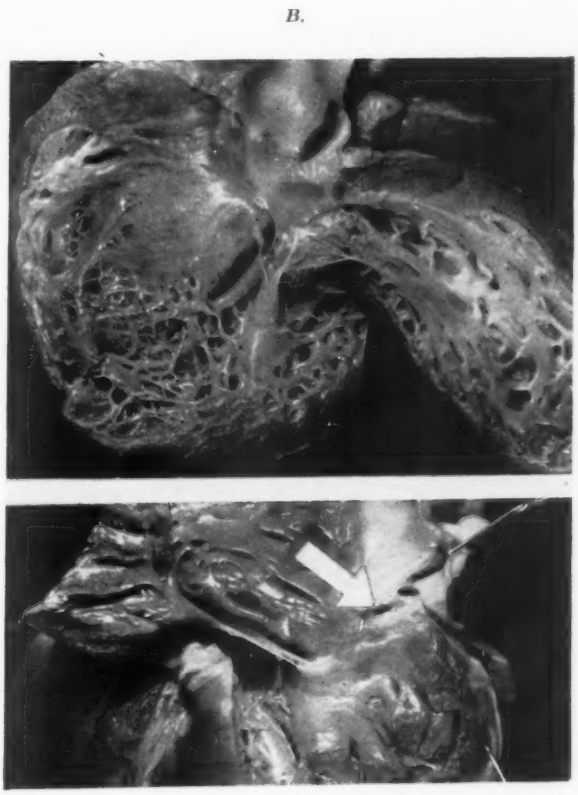


Fig. 4.—Case 2. *A*, Right ventricle. Arrow points to ostium of left coronary artery just above left sinus of Valsalva of pulmonary artery. *B*, Left ventricle. Hypertrophy and dilatation, endocardial fibrosis, atrophy of anterior papillary muscle. Note absence of vascular opening in left sinus of Valsalva of aorta.

in the thickened endocardium small white flecks could be seen. The myocardium of the left ventricle was 10 mm. in thickness near the base and became progressively thinner toward the apex, where it measured 2 millimeters. On section, there were gray patches beneath the endocardial lining and almost complete fibrous transformation in the aneurysmal portion near the apex. The outer portion of the myocardium was grayish-red, with a considerable amount of white flecking. The aortic valve was 3.2 cm. in circumference, and the right sinus of Valsalva gave origin to the right coronary artery, which was normal in appearance, course, and distribution. The left sinus of Valsalva contained no ostium.

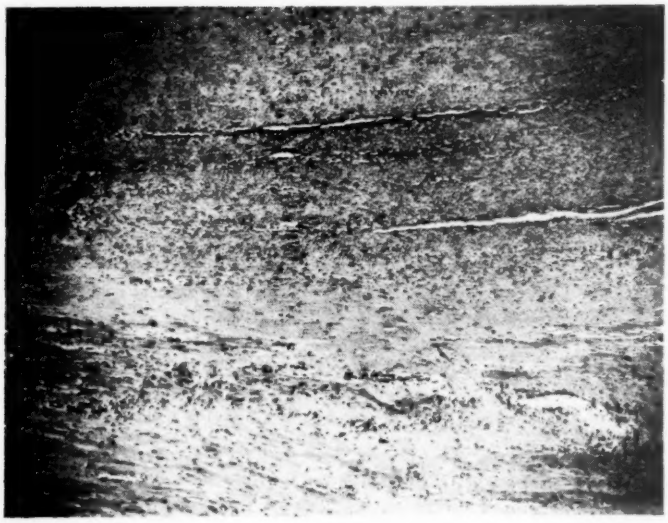


Fig. 5.—Case 1. Left ventricle, anterior wall. Extensive fibrous replacement of myocardium. Low power.

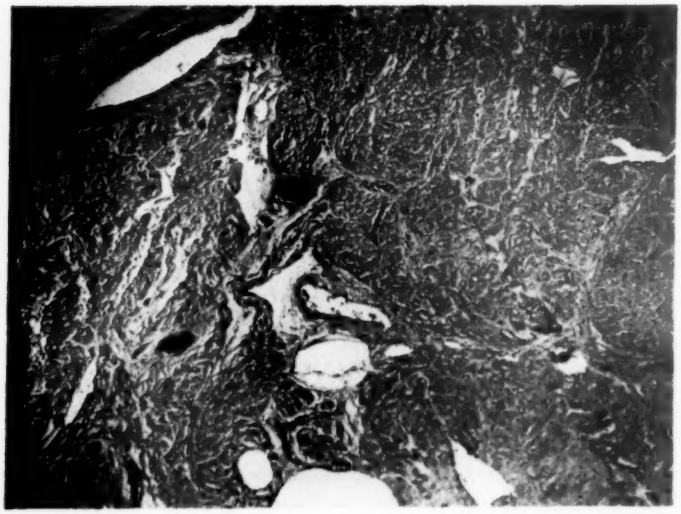


Fig. 6.—Case 1. Left ventricle, anterior wall. Dilated endothelial-lined myocardial sinuses. Medium power.

Microscopic Findings.—

Left Ventricle, Anterior Wall, Near Apex: The endocardium was greatly thickened, being composed of fibrous connective tissue and elastic fibers. The myocardium was thickened and largely replaced by vascularized fibrous connective tissue, especially near the endocardial surface (Fig. 5). Many muscle fibers showed loss of striation and nuclei. The fibrous septa were abnormally thickened. Some cells contained vacuoles, which did not take glycogen stain. There was occasional calcium deposition in the muscle and also hyaline and fatty changes. No cellular reaction was noted. There were numerous endothelial-lined sinuses (Fig. 6) scattered through the myocardium, chiefly near the endocardial surface, some of which contained blood. An occasional sinus appeared to open into the ventricular chamber. In the walls of the smaller arteries there was marked thickening of the intima, with proliferation of muscle and elastic fibers, and splitting of the internal elastic lamella. The intimal muscle fibers were oriented longitudinally and radially with respect to the lumen of the vessel. The media was very thin, being at most three or four fibers in width. The adventitia was thickened, with proliferation of fibrous connective tissue both within and outside this layer.

Anterior Interventricular Septum: The septum was thickened, with hypertrophy of muscle fibers. There were occasional foci of fibrosis and exaggeration of the connective tissue septa. Vascular changes were found similar to those described in the anterior wall of the left ventricle (Fig. 7).

Left Anterior Papillary Muscle: There was almost complete fibrous transformation, and in areas beneath the endocardium some individual muscle fibers seemed to have been replaced by calcium (Fig. 8).

Left Atrium: There was moderate fibrous and elastic endocardial thickening, with slight hypertrophy of the muscle fibers.

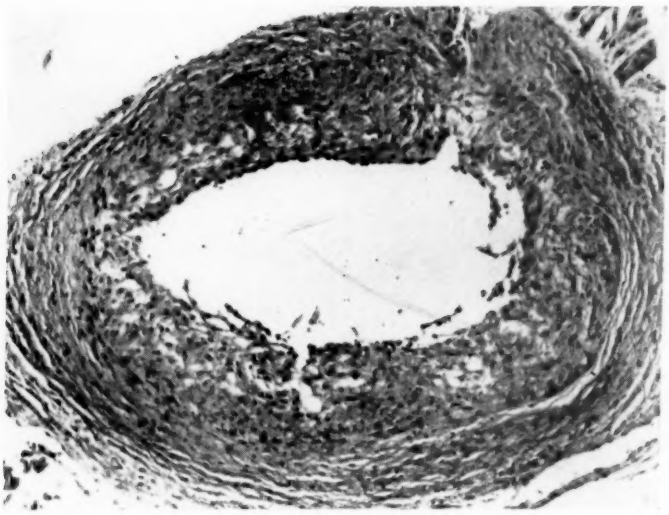
Left Posterior Papillary Muscle: Moderate fibroelastosis of the endocardium was present. There was slight fibrous replacement in the myocardial layer. Vessels were normal except for minimal intimal thickening of the smaller arteries. Myocardial sinuses were dilated.

No abnormalities were revealed in sections through the circumflex and anterior descending branches of the left coronary artery, the posterior descending branch of the right coronary artery, and several portions of the right ventricle and right auricle.

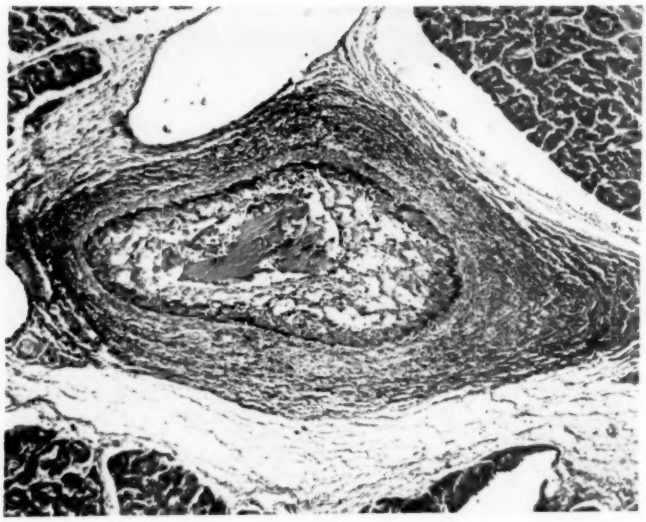
Diagnosis: (1) Origin of left coronary artery from pulmonary artery: dilatation and hypertrophy of left ventricle; myocardial fibrosis of left ventricle, with focal calcification, dilatation of myocardial sinuses, and musculoelastic intimal proliferation; atrophy of left anterior papillary muscle; diffuse fibroelastic thickening of endocardium of left ventricle; (2) bilateral bronchopneumonia; (3) atelectasis of left lung; (4) congestion and edema of liver; (5) hydrocele, left; (6) enlargement of thymus (37 grams).

CASE 2.—A 3-month-old female infant was admitted to the Mount Sinai Hospital with a history of grunting respiration since birth. Birth weight had been 7 pounds, 7 ounces. Pregnancy and delivery had been normal. At birth, several cutaneous hemangiomas were noted, which subsequently increased in size. Respirations had always been grunting in character, and there was transient cyanosis during crying. These symptoms increased in severity during the three days prior to admission.

Physical examination revealed a well-developed and nourished infant, who was pale, dyspneic, and cyanotic. The respirations were 70 per minute and grunting in quality. The alae nasi dilated on inspiration. The temperature was 99.6° Fahrenheit. Cutaneous hemangiomas were present over various parts of the body. The throat was congested and there were diminished breath sounds and dullness over the right lower lobe area. The heart was enlarged to the left on percussion, and sounds were of good quality with a rate of 180 per minute. No thrills or murmurs were heard. The liver edge was felt two fingerbreadths below the costal margin, and the spleen tip could be felt at the costal margin.

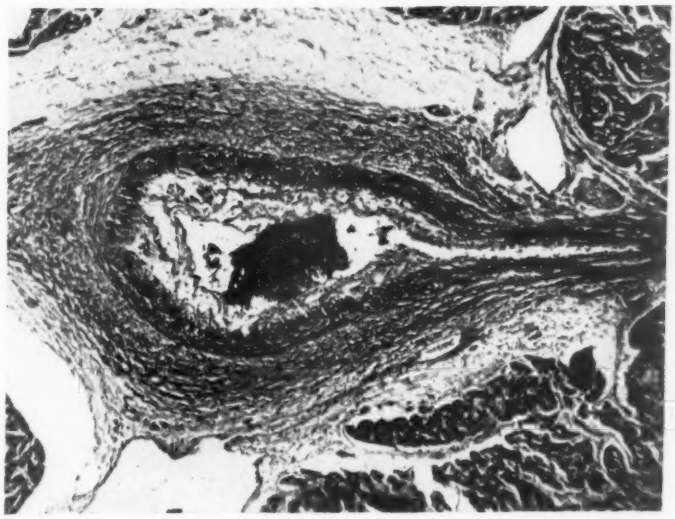


A.



B.

Fig. 7.—Case 1. Anterior interventricular septum. *A*, Small artery. Marked intimal thickening with thinning of media. Hematoxylin and eosin stain, medium power. *B*, Small artery, with thickened intima and fibrous thickening of adventitia. Weigert's elastic tissue stain and Van Giesen. Medium power. *C*, Same artery as shown in *B*. Phosphotungstic acid-hematoxylin stain. Medium power.



C.

Fig. 7.—*For complete legend, see opposite page.*

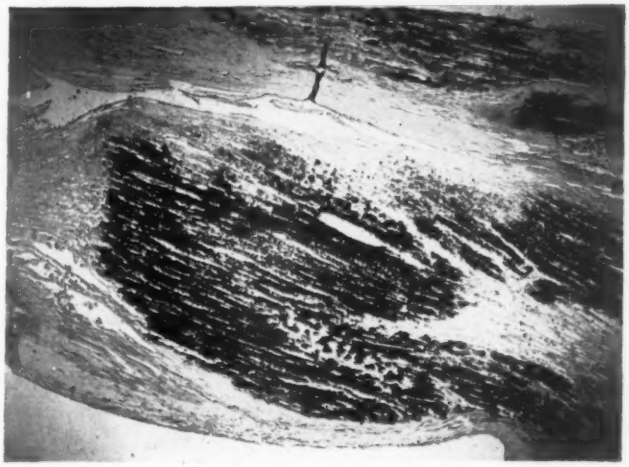


Fig. 8.—Case 1. Left anterior papillary muscle. Calcification of muscle fibers. Kössa stain. Medium power.

On admission, hemoglobin was 76 per cent (12.9 Gm.). White blood cells were 17,600 per cubic millimeter, with 49 per cent segmented and 4 per cent nonsegmented polymorphonuclears, 44 per cent lymphocytes, and 3 per cent monocytes. The urine was acid, contained a trace of albumin, and there were 30 white blood cells per high-power field in the sediment. X-ray examination of the chest on admission (Fig. 2, *A*) revealed the heart to be considerably enlarged to the left, with prominence of vessel markings in both lungs. Electrocardiogram on admission (Fig. 2, *B*) indicated sinus tachycardia (rate 180), tendency to left axis deviation, moderately high voltage in Leads II and III, slightly depressed RS-T_1 and RS-T_2, inverted T_1 and T_2 and biphasic T_4.

The patient was placed in an oxygen cubicle, given 10,000 units of penicillin every three hours, and was rapidly digitalized. On this regimen, the symptoms of congestive heart failure disappeared within three days. Six weeks after admission, an attack of dyspnea, tachycardia, and acute enlargement of the liver occurred and responded well to digitalization. Because of the presence of many cutaneous hemangiomas, it was thought that a similar condition within the heart might account for the cardiac symptoms, and for this reason 1,200 roentgen units were administered over the left chest. Serial electrocardiograms revealed a bifid P_1; the RS-T segments in Leads I and II became less depressed, and T_2 became upright. During the ninth week of hospitalization, dullness on percussion of the entire left chest was noted, and an x-ray film was thought to reveal pleural effusion. On aspiration of the left chest, a small amount of blood-tinged, straw-colored fluid was withdrawn, which was sterile on culture. In the thirteenth week of hospitalization, there was rise in temperature to 104.2° F., which was accompanied by dyspnea and tachypnea. Despite therapy directed to combat congestive heart failure and infection, the patient rapidly failed and died after three months of hospitalization and at the age of six months.

Autopsy.—Autopsy* was performed fifteen hours after death. Findings were as follows: The heart weighed 100 grams (average normal, 34 grams). The pericardial sac contained a few cubic centimeters of clear straw-colored fluid, and the epicardial surface was smooth and glistening. The heart was strikingly enlarged, with the left border prominent and bulging. On the anterior wall of the left ventricle was an extensive, delicate vascular network which imparted a blue color to this area. Prominent vascular channels were noted also over the anterior surface of the pulmonary artery. The right auricle was slightly dilated. The foramen ovale was closed. The tricuspid valve was 5 mm. in circumference, and the leaflets were delicate and transparent. The right ventricle was slightly dilated and hypertrophied; its wall measured up to 5 mm. in thickness. The trabeculae carneae were prominent, and the endocardium was thin and transparent. The myocardium of the right ventricle appeared normal on section. The pulmonic valve was normally formed and measured 3 cm. in circumference. Four millimeters above the left sinus of Valsalva of the pulmonary artery was the widely patent ostium of the left coronary artery (Fig. 4, *A*). Just distal to the orifice, this artery branched in the usual fashion and had a normal course and distribution. The vessel was normal in width, the lumen patent, and the intima delicate and smooth. The ductus arteriosus was obliterated. The left atrium was normal except for slight endocardial thickening. The mitral valve was normally formed; the ring measured 5 cm. in circumference. The left ventricle (Fig. 4, *B*) was greatly dilated and hypertrophied and was converted into a wide aneurysmal sac with a bulging anterior wall and apex. At its base the posterior wall measured 10 mm. in thickness. Toward the anterior wall and the apex the wall became progressively thinner and measured only 1 to 2 mm. in the thin bulging area which was beneath the delicate vascular network observed on the epicardial surface. At its thinnest portion, the wall was transformed into fibrous tissue. The endocardium of the left ventricle was grayish-white, thickened, and lusterless, and beneath it were seen a few small flat yellow patches. The trabeculae carneae were thickened and prominent. The anterior papillary muscle was flat and white, and there were many white flecks in the surface. The posterior papillary muscle was only slightly flattened. The interventricular septum bulged toward the right. The aortic valve was normally formed; the ring measured 3 cm. in circumference. The right coronary ostium

*By Dr. L. Strauss.

was encountered in its usual position just above the right sinus of Valsalva of the aorta. The right coronary artery was normal in size, course, and distribution. There was no vascular opening in the left sinus of Valsalva.

Microscopic Findings.—

Left Ventricle, Anterior Wall: There was marked thickening of the endocardium which consisted principally of fibrous and elastic tissue. Chiefly near the endocardial surface were extensive areas of fibrous replacement of myocardium. Many muscle fibers showed loss of nuclei and striations. Capillaries and endothelial-lined sinuses were numerous; some of the latter appeared to enter the ventricular chamber. No cellular reaction was seen. The small arteries appeared normal.

Interventricular Septum, Anterior: The endocardium was thickened and fibroelastic. Most arteries showed marked intimal thickening, composed of muscle and elastic fibers. In some portions, the vessels were almost occluded by this process. The internal elastic lamella was shredded. The inner portion of the intima was in the form of a meshwork which did not stain with Sudan III. The media was much thinned. The adventitia was thickened and composed of a loose fibrillar network. There was moderate increase in perivascular connective tissue.

Left Ventricle, Posterior Wall: The endocardium was moderately thickened, with elastic and connective tissue fibers. There was extensive scarring of the myocardium; some areas showed vacuolization and loss of nuclei and of striations of muscle fibers. Areas of calcification were present within the myocardium and trabeculae. Myocardial sinuses were dilated.

Left Anterior Papillary Muscle: There was marked atrophy and almost complete replacement by scar tissue which contained large numbers of elastic fibers. Many foci of calcification were present throughout. The endocardium was moderately thickened.

Left Posterior Papillary Muscle: The endocardium was thickened and fibroelastic. There was moderate diffuse fibrosis of the myocardium, particularly beneath the endocardium. The vessels were normal.

No abnormalities were revealed in sections through the circumflex and anterior descending branches of the left coronary artery, the posterior descending branch of the right coronary artery, and several locations in the right ventricle and both auricles.

Diagnosis: (1) Origin of left coronary artery from pulmonary artery; dilatation and hypertrophy of left ventricle; myocardial fibrosis, left ventricle, with focal calcification, dilatation of myocardial sinuses, and musculoelastic intimal proliferation; atrophy of left anterior papillary muscle; fibroelastic thickening of endocardium of left ventricle; (2) atelectasis and confluent bronchopneumonia of left lung; (3) congestion of liver; (4) multiple hemangiomas of skin; (5) follicular cysts of ovaries.

SUMMARY OF THE LITERATURE

A summary of similar cases reported in the literature in infants and adults is given in Tables I and II, respectively.

The publication of these cases has encouraged two authors to describe patients in whom this diagnosis was suggested during life without post-mortem confirmation. Brown[25a] reports the case of a 2-year-old boy with exertional dyspnea, cardiac enlargement to the left, gallop rhythm, and electrocardiographic changes suggestive of myocardial anoxia. At last report,[25b] the child was 13 years of age, and the clinical and electrocardiographic changes persisted. Diaz'[26] case was a 42-year-old man who, since infancy, had had exertional precordial pain and cyanosis which was not relieved by vasodilator drugs. The heart was enlarged to the left and the electrocardiogram revealed left bundle branch block,

TABLE I. SUMMARY OF REPORTED CASES OF ORIGIN OF LEFT CORONARY ARTERY FROM PULMONARY ARTERY IN INFANTS

NO.	AUTHOR	AGE (MO.) SEX	CLINICAL COURSE	PATHOLOGIC FINDINGS	REMARKS
1	Abrikossoff[1]	5½ F	Not given	Hypertrophy and dilatation of left ventricle with aneurysmal dilatation; endarteritis of coronary vessels; calcific replacement of myocardium; flattened left anterior papillary muscle	Believes anomaly due to misplaced coronary artery anlage
2	Cazzaniga[3]	4 F	Sudden death; always in good health previously	Hypertrophy and dilatation of left ventricle, with endocardial thickening; diffuse fibrosis of left ventricle and septum; perivascular cellular infiltration; no changes in vessels; left anterior papillary muscle atrophied and scarred	Believes that an abnormal formation of the septum primum unlikely in the etiology of this anomaly
3	Heitzmann[4]	3½ F	Died in attack of syncope and cyanosis	Hypertrophy and dilatation of left ventricle, with aneurysmal dilatation; flattening of left anterior papillary muscle; calcification in anterior wall of left ventricle and anterior papillary muscle; myocardial necrosis and fibrosis; endocardial thickening	Likens these changes to those found in coronary sclerosis
4	Kiyokawa[5]	4*	Attacks of cyanosis and convulsions	Heart greatly enlarged; left ventricle hypertrophied and dilated, with aneurysmal dilatation at apex; septum deviated to right; focal areas of fibrosis, necrosis, congestion, and round-cell infiltration; vessels normal	Hydropericardium; hydrothorax; congestion of lungs and liver
5	Krumbhaar[6]	10 F	Not given	Heart weight, 136 grams (normal, 39); hypertrophy and dilatation of left ventricle; vacuolar degeneration and areas of fibrosis; marked fibrosis of left anterior papillary muscle and anterior portion of septum	Believes that coronary anomaly did not cause pathologic changes

6	Heidloff[7]	7½ F	Dyspnea for 4 mo.; retarded development; sudden death	Heart weight, 127 grams (normal, 27); deposits of fibrin over epicardium of left ventricle; right heart slightly enlarged; left auricle thickened and dilated; left ventricle dilated but not hypertrophied; aneurysmal dilatation of left ventricle, with calcification; vessels normal	Believes enlargement of heart due to hypertrophy of right ventricle; left lung atelectatic
7	Abbott[8]	3*	Hoarseness	Excessive dilatation and hypertrophy of left ventricle	
8	Scholte[9]	2½ F	Bronchopneumonia	Dilatation and hypertrophy of left ventricle; fibrosis, fatty changes, focal areas of necrosis, and calcification in left ventricle; flattening of left anterior papillary muscle; thickening of endocardium	Likens these changes to those found in coronary occlusion
9	Bland, White, and Garland[2]	3 M	Attacks of dyspnea, sweating and pallor for 2 wk., precipitated by nursing; x-ray, diffuse enlargement; ECG, low voltage, inverted $T_{1,2,3}$	Heart weight, 91 grams (normal, 25); dilatation and hypertrophy of left ventricle, with increased thickness due to increase in number of muscle fibers and fibrosis; subendocardial fibrosis; hydropic changes in some muscle cells	Likens lesions to those found in coronary sclerosis; ECG changes also similar; attacks of sweating and pallor, thought to have been anginal in nature
10	Sanes and Kenney[10]	3 M	Vomiting for 3 wk.; difficulty in breathing for 3 days; x-ray, enlarged heart	Heart weight, 95 grams (normal, 25); dilatation and hypertrophy of left ventricle, with aneurysmal dilatation at apex; fibrosis in myocardium of left ventricle; calcification and marked fibrosis of left anterior papillary muscle; deviation of septum to right; areas of necrosis in myocardium of left ventricle	Hydropericardium; likens myocardial changes to those due to excess amount of lactic acid in blood
11	Bartsch and Smekal[11]	3 M	Not given	Dilatation and hypertrophy of left ventricle; aneurysmal dilatation at apex; deviation of septum to right; endocardium thickened, with round-cell infiltration; foci of fibrosis throughout, with localized calcification at apex and anterior wall of left ventricle	

*Set not given.

TABLE I. SUMMARY OF REPORTED CASES OF ORIGIN OF LEFT CORONARY ARTERY FROM PULMONARY ARTERY IN INFANTS—CONT'D

NO.	AUTHOR	AGE (MO.) SEX	CLINICAL COURSE	PATHOLOGIC FINDINGS	REMARKS
12	Haferkorn[12]	4 F	Wheezing and cough since age of 7 wk.; difficulty in breathing at 3½ mo.; attacks of dyspnea, with anxious facial expression; x-ray, enlargement of heart to left	Dilatation and hypertrophy of left ventricle, with some enlargement and hypertrophy of right ventricle	Compression atelectasis of left lower lobe; cites symptom complex, clinical findings, and believes this to be a clinical entity
13	Linck[13]	8 F	Not given	Heart weight, 110 grams (normal, 37); hypertrophy and dilatation of left ventricle; areas of myocardial fibrosis, with hyaline changes in muscle fibers	
14	Chown and Schwalm[14]	5 M	Attacks of pallor, cough, cyanosis, fever	Heart weight, 70 grams (normal, 29); veins and myocardial sinuses dilated; hypertrophy and dilatation of left ventricle, with thickening of endocardium; left anterior papillary muscle vestigial; degeneration in myocardium of both ventricles, with large amount of fibrous replacement in left ventricle	Hydropericardium; congestion of liver; believes anomaly due to defective placement of coronary artery anlage
15	Barnard[15]	5 F	At age of 19 wk., unable to swallow and gain weight; bulge in left chest; x-ray, enlargement of heart	Hypertrophy and dilatation of left ventricle; endocardial thickening, especially over trabeculae carneae; patchy necrosis and fibrosis, particularly subendocardially; coronary vessels normal	Atelectasis of left lower lobe; congestion of spleen and liver; believes anoxic changes may have started in fetal life

16	Benešová[16]	2½ F	Dyspneic and cyanotic; x-ray, enlargement of heart to left; died suddenly	Balloonlike enlargement of left ventricle, with atrophied papillary muscles, thickened endocardium; aorta slightly narrower than pulmonary artery; endocardial thickening, consisting of loose connective tissue and fibroblasts; necrosis, fatty infiltration found particularly in inner half of myocardium; no inflammatory reaction found; calcification in anterior wall	Injection of right coronary artery revealed collateral circulation with left; musculoelastic intimal proliferation in some arteries
17	Soloff[17]	4½ M	Attacks of pain, cyanosis, dyspnea, precipitated by feeding	Heart weight, 120 grams (normal, 30); dilated veins beneath epicardium of left ventricle; normal coronary artery distribution; no intercommunication found; right coronary ostium smaller than normal, left coronary ostium wider; embryonic sinusoids present; acute hydropic, fatty, and necrotic changes in myocardium with fibrosis and calcification	Believes this represents a syndrome in infants, that the anomaly is due to misplacement of the coronary artery anlage, and that the thinness of the media of the left coronary artery is due to diminished intraluminal pressure
18	Proescher and Baumann[18]	13 F	Fever, wheezing, cough, anorexia, vomiting; left chest splinted; sudden death	Heart weight, 180 grams (normal, 42); visceral pericardium thickened over anterior left ventricle; left ventricle dilated and hypertrophied, with deviation of septum to right; left coronary ostium narrower than normal; embryonal sinusoids present; muscle fibers atrophic, elongated, fragmented, with fibrous tissue replacement; remnants of degenerated, necrotic, calcified muscle fibers present; endocardium thickened; perivascular fibrosis and intimal thickening	Left pyothorax; atelectasis of left lower lobe; believes persistence of sinuses indicates developmental failure; remarks that these cases occur in females twice as often as in males

Since the submission of this report, Eidlow and Mackenzie (Am. Heart J. **32:** 243, 1946) described the case of a female infant, normal at birth, who, at the age of 3 months, began to have attacks of dyspnea, choking associated with feeding, and paroxysms of cyanosis, dyspnea, and tachycardia. On x-ray examination, the heart was enlarged to the left and right, and there was partial atelectasis of the right upper lobe. An electrocardiogram revealed inversion of T_1 and T_2. These clinical, x-ray, and electrocardiographic findings directed the authors to the diagnosis of anomalous origin of the left coronary artery. The infant died at the age of 4 ½ months with signs suggesting pneumonia. At autopsy the heart weighed 85.3 grams (normal, 27). The left coronary artery arose from the pulmonary artery. All heart chambers were dilated, and the left ventricle was markedly dilated and hypertrophied, with fibrosis of the inner third of the wall. There was atrophy and vacuolization of muscle fibers. No embryonic sinusoids were seen. The endocardium of the left ventricle was thickened and fibrotic. There was slight medial thickening of the smaller coronary artery branches but no other abnormalities of the vessels. Pneumonia of the left lung and atelectasis of the right upper lobe were present.

TABLE II. SUMMARY OF REPORTED CASES OF ORIGIN OF LEFT CORONARY ARTERY FROM PULMONARY ARTERY IN ADULTS

NO.	AUTHOR	(YR.) SEX AGE	CLINICAL COURSE	PATHOLOGIC FINDINGS	REMARKS
1	Abbott[8]	64 F	Not given	Hypertrophy, fibrosis and fatty changes; right coronary artery expanded near origin into a thick-walled loop and tortuous and thick-walled throughout its course; left coronary artery thin-walled, apparently originating in a sinus from the pulmonary artery	
2	Kockel[19]	38 M	Episodes of precordial pain for a few years; died suddenly	Hypertrophy and dilatation of left ventricle; right coronary artery widened; no communication demonstrable between the coronary arteries; two fibrotic patches near bundle of His	Believes right coronary artery had assumed some function of the left
3	Rübberdt[20]	27 M	Died suddenly while working with pneumatic drill	Hypertrophy and dilatation of left ventricle; fibrous replacement of muscle fibers; no acute inflammation or degeneration found; right coronary artery widened; left coronary artery does not supply as much of myocardium as normally	Believes the sudden death due to anoxemia, brought on by demand for more oxygen, with supply limited by the anastomotic connection between right and left coronary arteries
4	Dietrich[21]	53 M	Sick as child; thought to have had valvular disease; hypertension and auricular fibrillation present; episodes of angina	Large areas of subendocardial calcification; dilatation and hypertrophy of both sides of heart; both coronary arteries tortuous and dilated but distribution normal; right coronary artery sclerotic only near origin; intimal thickening in left coronary artery found only in myocardial branches	Believes dilatation and tortuosity of coronary arteries to be manifestation of adaptation, allowing individual to survive

5	Orsós[22]	17 F	Sudden death after exertion	Heart weight, 390 grams; dilatation of both ventricles; myocardial fibrosis of left ventricle, with appearance that of infarction; normal course of coronary arteries	Believes increased demands at time of puberty precipitated terminal episode
6	Ruddock and Stehly[23]	30 M	Sudden death during exertion	Heart normal in size; right coronary artery dilated, supplying all portions of myocardium except in the area of the left anterior descending artery; anastomoses between arteries demonstrable; no myocardial changes seen	Believes dilatation of right coronary artery an adaptation of coronary circulation and that myocardial damage was prevented by anastomoses
7	Helpern[24]	32 M	Sudden death; no known history of heart disease; death possibly due to barbiturate poisoning	Heart weight, 450 grams; dilatation and hypertrophy of left ventricle, with thickened endocardium; patch of fibrosis at apex of left ventricle; right coronary ostium greatly enlarged; both coronary arteries dilated and tortuous throughout their courses; dilated sinusoids in myocardium; only anterior wall of left ventricle supplied by left coronary artery; no anastomoses found between coronary arteries; some arteries in left ventricle show musculoelastic intimal proliferation; slight dilatation and hypertrophy of right ventricle	

with increased P-R intervals and RS-T elevations on exercise. Both authors, while expressing confidence in their diagnosis, call attention to the difficulties in ruling out other possible causes for the clinical findings. The long history, starting in infancy, is not reminiscent of any of the autopsied cases reported in adults, and the electrocardiographic changes are not similar to those found in the second case reported here nor the case of Bland, White, and Garland.[2]

Two cases have been reported in which the right coronary artery arose from the pulmonary artery, while the left coronary artery arose from the aorta. The patients died at 30 and 61 years of age, respectively, from unrelated causes, and in neither instance was there evidence of myocardial disease. In both instances, the left and right coronary arteries were dilated. In the first patient,[27] anastomoses between the branches of the vessels were detected. The right coronary artery was thin-walled and appeared rather like a vein. In the other instance,[28] the left coronary artery was thought to assume some of the function of the right coronary, and collateralization of the left coronary artery was abundant.* It may be assumed that when the right coronary artery is supplied with blood directly from the pulmonary artery, sufficient oxygen is available to allow the myocardium supplied by the right coronary artery to function, and that collateralization results as an adaptation of the coronary circulation to this unusual condition.

Two cases have been reported in which both coronary arteries arose from the pulmonary artery. In Grayzel and Tennant's[29] case, other cardiac abnormalities were present, the infant lived only a few hours, and the heart was not enlarged. Limbourg's[30] case had no associated cardiac anomalies and lived for ten days. The heart was normal in size and the left ventricle was slightly enlarged, with fatty infiltration of the myocardium. Apparently, when both coronary arteries receive blood from the pulmonary artery, there are insufficient compensatory factors available to maintain life beyond a few days.

DISCUSSION

Introduction.—The average blood pressure within the right ventricle is normally approximately one-sixth of that in the left ventricle. Thus, in the cases here referred to, the blood pressure within the left coronary artery is considerably below normal. The normal average oxygen content of blood within the right ventricle is approximately 12 to 14 volumes per cent, while the oxygen content of arterial blood is approximately 19 volumes per cent. The normal arteriovenous difference of the greater circulation (between aorta and right ventricle) is therefore 5 to 7 volumes per cent. The normal arteriovenous difference of the coronary circulation (between aorta and coronary sinus) is 10 to 15 volumes per cent. Not only does cardiac muscle respond by ceasing to function normally

*Since the submission of this report, an unpublished third case has been furnished, through the courtesy of W. A. Bennett, from the records of the Mayo Clinic. The patient was a 74-year-old man who died in congestive heart failure. The heart weighed 550 grams, and there was an old infarct at the apex with focal fibrosis of the septum. The identity of the right coronary artery was established only by microscopic examination, inasmuch as the gross appearance was that of either a vein or an artery. There was more marked sclerosis of the left coronary artery than of the right. No collateralization was mentioned.

when a slight oxygen debt is incurred, but also as the ventricle dilates and the muscle fibers are lengthened, more oxygen is required for the same amount of work.[31] Therefore, in the cases reported here, it may be assumed that the heart was deprived of sufficient oxygen for normal function.

Judging from the relative infrequency with which symptoms are mentioned before the age of 2 months, it would seem that for the first weeks of life the blood perfusing the left coronary artery is sufficient to maintain some degree of integrity of the myocardium. However, the growth of the infant imposes increasing demands which cannot be met, and the heart begins to fail. It is also possible that the gradual obliteration of the ductus arteriosus, usually complete at about the third month,[32] withholds an additional source of oxygen from the left coronary circulation. According to Wiggers,[33] the heart muscle will hypertrophy upon constant stretching of the muscle fibers, as occurs in heart failure, and also when the heart is required to work nearer its reserve limit (as when more work is demanded without a corresponding increase in oxygen supply); both of these situations obtain in the condition we are discussing. Moreover, as Wearn[34] has demonstrated, the hypertrophied heart suffers a relative reduction in its blood supply, for the vascularization per unit weight falls and metabolic exchange is hindered. Anoxia leads inexorably to the fatal termination. It therefore appears that the pathologic changes found at necropsy represent the end stage of severe chronic anoxia of that portion of the heart furnished blood by the left coronary artery.

Etiology.—The coronary arteries are first seen as outpouching endothelial buds in the wall of the aortic bulb. Later, the bulbar septum forms to separate the aorta from the pulmonary artery. Two theories have been presented to explain the cause of the anomalous origin of one or both coronary arteries from the pulmonary artery:[1] (1) that the coronary artery anlage arises in the wrong location in the wall of the aortic bulb, so that the normally forming septum includes the coronary artery within the pulmonary artery instead of the aorta and (2) that the coronary artery anlage is normally disposed, but the bulbar septum forms in the wrong plane and incorporates one or both coronary arteries within the pulmonary artery. Cases have been reported in which the anomalous origin of the left coronary or of both coronary arteries from the pulmonary artery was associated with other cardiac defects,[35] and these would seem to be examples of an abnormally forming septum, as in the second theory mentioned previously. However, in all the cases summarized in Tables I and II, no associated cardiac abnormalities were reported, so it is most probable that these instances were the result of an abnormal position of the coronary artery anlage. The greater incidence of anomalous origin of the left coronary artery, as compared with the right, may be explained by the proximity of the left sinus of Valsalva of the aorta to the septum of the truncus arteriosus, with the result that a small displacement of its anlage would cause the left coronary artery ostium to fall within the pulmonary artery. The corresponding right sinus of Valsalva is much further from the septum, so that a considerable displacement of the right coronary artery anlage would be required to cause the anomalous origin of this vessel from the pulmonary artery.

Sex Incidence.—Proescher and Baumann[18] called attention to an apparent sex predilection of this anomaly. In the literature they cited, there were twice as many female as male subjects. Of the cases in this series where sex was mentioned, there were fourteen female and eleven male patients, including twelve female and six male infants and two female and five male adults.

Clinical Course.—It will be noted that several of these infants died suddenly, while others had repeated attacks of cyanosis and dyspnea, particularly associated with nursing. The latter symptoms prompted Bland, White, and Garland[2] to suggest that these were episodes of angina pectoris due to transient myocardial anoxia. Haferkorn[12] and, later, Soloff[17] felt that when this syndrome was associated with x-ray evidence of cardiac enlargement to the left and consistent electrocardiographic findings, the diagnosis could be made during life. In the first case reported here, there was no history of these transient attacks, while in the second case there had been transient cyanosis during crying since birth.

In several cases, the left ventricle was found to compress the left lung so that there was atelectasis of the left lower lobe. In each of the cases reported here, the left lung was collapsed due to compression by the enlarged left ventricle. The atelectasis undoubtedly contributed to the anoxemia.

Of the seven adults, four died unexpectedly, and three of these had no reported previous illness or disability. It is not clear just how much the vascular anomaly contributed to the clinical findings in Dietrich's[21] case. In Kockel's[19] case, two fibrotic patches near the bundle of His may have had some significance. In the latter instance, the patient had periodic precordial pain for several years.

Electrocardiographic Changes.—Bland, White, and Garland[2] presented the only electrocardiogram in the literature in a case of this type. There was low voltage and T-wave inversion in all leads, without axis deviation. Case 2 of this report revealed high voltage in Leads II and III, RS-T and T-wave changes characteristic of myocardial anoxia, and a tendency toward left axis deviation.

Pathology.—

Introduction: Any interpretation of pathologic findings in infants is tempered by the many imponderable physiologic factors attending growth. No doubt the tissues of an infant will respond to a given stimulus in a different manner than the tissues of an adult. For instance, the hypertrophy associated with congenital valvular lesions may involve a fourfold increase in the size of an infant heart, a situation almost unknown in adults even with heart disease of many years' standing. While stimuli are acting upon them, the tissues have certain demands which vary from age to age, and thus, in these infants, the reaction of the myocardium to chronic anoxia will be different in form and in tempo.

Duration of the Pathologic Changes: Barnard[15] believes that the pathologic changes described in these cases may have begun in fetal life. Quoting Barcroft's studies revealing that inferior and superior caval blood streams take separate pathways in the fetal circulation, he maintains that even before birth

there would be less oxygen provided to the left coronary than to the right coronary artery. However, the youngest patient in this series was 2½ months old at death, and since the findings were compatible with a process of this duration, it is unnecessary to attribute a greater age to the pathologic process. Also, in Limbourg's[30] patient, who died at 10 days of age, both coronary arteries arose from the pulmonary artery, yet the heart showed minimal changes. It is therefore unlikely that damage in these cases developed prenatally.

Pathology and Age at Death: The age of these patients at death is a matter of great interest. Of the twenty-seven cases, twenty were 2½ to 13 months old at death. The seven adults were 17 to 64 years of age at death. Why did the majority of these patients die in early infancy, and why did the remainder, having survived early infancy, live until at least early adult life?

It is obvious that, with unimportant variations, the morbid lesions found in the two cases presented here duplicate those reported in the eighteen other infants.

One is impressed that the hearts in the adult group had certain characteristics in common. The right coronary artery was enlarged in most cases so that in some it assumed a cirsoid form. In all except two cases, the left coronary artery was also enlarged. Also, in four of the seven cases, the right coronary artery appeared to have taken over the greater part of the coronary circulation. Did these individuals survive to adult life because of congenital variations in the distribution of the coronary arteries, or are these variations a manifestation of adaptation which allowed these few individuals to survive their infant years? Acknowledging the rarity of such congenital variations on the one hand and the well-known development of collateral circulation in disease of the coronary arteries on the other, the latter alternative seems to be correct.

In three of the seven adults, there was no change reported in the myocardium or the endocardium, so that in all probability the collateralization of the coronary circulation must have begun in early infancy, before any irreversible changes had taken place.

Hypertrophy and Dilatation: Although there is no record of blood pressure in these cases, it is unreasonable to assume that hypertension entered into the pathogenesis of the myocardial lesions. The hearts were generally four times the normal weight, and dilatation and hypertrophy were confined for the greatest part to the left ventricle. Possible physiologic processes underlying the hypertrophy have been outlined in the foregoing. The increased weight of the hearts is ascribable to hypertrophy of muscle fibers and increase in fibrous connective tissue. Almost all the reported cases were described as being in congestive heart failure at some time.

The right ventricle was dilated in several instances. This can be attributed to the failure of the left ventricle and to the functional insufficiency of the left anterior papillary muscle. It is also possible that the marked bulging of the interventricular septum to the right, mentioned in several cases, aggravated the already existing strain on the right ventricle.

Localization of the Lesions: Among the twenty cases reported in infants, including the two present cases, there was a striking uniformity in the distribution of the lesions. The effects of long-standing anoxia were manifest in those portions of the heart supplied by the left coronary artery: the anterior portion of the interventricular septum and the anterior and lateral walls of the left ventricle.[36] The majority of authors mentioned shrinking, fibrosis, and calcification of the left anterior papillary muscle, which not only derives its blood supply solely from the left coronary artery, but, from the standpoint of the coronary vascular tree, is at the greatest distance from the ostium of the left coronary artery.[36] Where the right coronary artery could be expected to assume part of the burden, such as in the posterior wall of the left ventricle, the changes, while still present, were of lesser degree; in the right ventricle, supplied completely by the right coronary artery, there were no abnormal findings except for slight dilatation and hypertrophy.

Calcification: In twelve of the twenty-seven cases, calcification of the myocardium was described. This usually took the form of actual replacement of individual muscle fibers and was most marked in the left anterior papillary muscle. In the two cases reported here, calcification was most marked in the areas of the greatest scarring. We agree with Abrikossoff[1] and believe that calcification follows necrosis of muscle fibers.

Whereas calcification of the myocardium due to coronary artery disease is only occasionally found,[37] it is frequently found in lesions such as congenital atresia or stenosis of the aortic valve in children, within areas of scarred myocardium.[38] The myocardium in children appears more prone to calcify.[38] Perhaps this observation is connected with the finding that values for serum calcium, inorganic phosphorus, and phosphatase are significantly higher in children than in adults.[39]

Endocardial Thickening: In all the cases reported in infants, there was marked thickening of the endocardium, composed of fibrous and elastic tissue. The localization of this process within the left ventricle and the coincident changes in the underlying myocardium leave little doubt as to the common etiology. Fibroelastic thickening of the endocardium, termed variously fetal endocarditis[40] and endocardial fibroelastosis,[41] has been reported in infants with and without myocardial changes and with and without valvular disease. Several cases have been reported in association with congenital aortic atresia and stenosis,[42] where both coronary arteries received all or most of their blood supply from the pulmonary artery through the ductus arteriosus. It would be anticipated that under these circumstances the left ventricle would suffer the most severe anoxia, since it is under greater work demands than the right ventricle. In the cases reviewed by Farber and Hubbard,[42] the endocardial and myocardial changes were confined to the left ventricle and were very similar to those found in the cases presented here. The likelihood therefore exists that at least some of the cases reported as fetal endocarditis and endomyocarditis were indeed due to anoxic changes caused by perfusion of the coronary arteries with partly oxygenated blood at low pressure. Gross[40] believes that the endocardial thickening is primary and

serves to seal off the vascular channels between the chamber of the ventricle and the myocardium, thus causing stasis in the myocardial sinuses and anoxia of the myocardium. In the cases reported here, anoxia seems to be sufficient reason for the myocardial and endocardial changes.

Collateral Circulation: Lowe[43] has found that when occlusive disease alters the pressure gradient between branches of the same artery, redistribution of blood supply is encouraged, and new routes and anastomotic channels develop rapidly. By the same token, collateralization in these infants should be enhanced because of the low pressure within the left coronary artery and its branches associated with normal pressure within the right coronary artery. This stimulation would be apparent initially only in the peripheral portions of the area supplied by the left coronary artery and would continue as long as the pressure differential existed. Apparently, in the adults in whom the right coronary artery was found to supply almost all the heart musculature, this process of collateralization had reached the maximum potential, in that the pressure within the distal branches of the right coronary collaterals approached the pressure within the adjacent remaining branches of the left coronary artery. In the infants, such collateralization may not have been evident because of the rapid progressive course.

Myocardial Sinuses: Several authors[14,17,18,24] have called attention to the presence of endothelial-lined, blood-filled spaces in the myocardium in these cases and have expressed the opinion that there is abnormal persistence of the embryonic sinusoids which provide circulation in the myocardium during early fetal life. In both the cases presented here, dilated myocardial sinuses were found in the wall of the left ventricle, but in no other location, and several of these spaces appeared to communicate with the ventricular cavity.

Wearn[34] has shown that in addition to the Thebesian vessels, there are other communications between the lumen of the heart and the vessels within the wall. Under ordinary circumstances, there is little blood flow in these vessels because of the approximate equality of pressures within the chamber of the ventricle and the mural vessels. However, in this situation, where the pressure within the left ventricle is much higher than that within the myocardial vessels of the left ventricle, it is reasonable that there should be flow of blood through the Thebesian as well as the arterioluminal and sinusoido-luminal vessels and therefore possible that the myocardial sinuses seen histologically in these cases represent functioning communications.

Changes in Arteries: In both of the cases reported in this paper, in the smaller arteries in the wall of the left ventricle and the interventricular septum there was found intimal hyperplasia consisting of proliferation of muscle and elastic fibers, the former being oriented radially and longitudinally with respect to the vessel wall. In places, the lumen was almost occluded by the intimal proliferation. The internal elastic lamella was shredded. The media was thin, being reduced to the thickness of three or four fibers at some places. It is possible that the medial thinning may have been due in part to the intimal

thickening itself, the media being compressed by the growing intima. There was increase in fibrous connective tissue in the adventitia and perivascular zone. The larger arteries appeared normal. In the posterior wall of the left ventricle, minimal intimal thickening was present. No remarkable vascular changes were seen in the right ventricle.

These findings are similar to those illustrated by Abrikossoff,[1] who described the process as productive endarteritis and considered it to be secondary to the myocardial changes. Benesová[16] described vascular changes in her case which were similar in type and distribution to those we have described. Dietrich's[21] case was an adult and showed severe arteriosclerosis of the larger branches of the right coronary artery, while the smaller branches were normal. On the other hand, while the larger branches of the left coronary artery were normal in appearance (except for dilatation), the myocardial branches exhibited the same changes that were found in the cases reported here. Helpern's[24] case showed similar changes in the myocardial branches of the left coronary artery.

Soloff[17] described dilatation of the left coronary artery, with thinning of the media, and considered this a response to diminished intraluminal pressure. He did not mention intimal changes.

Zinck,[44] describing normal vessels in infant hearts, mentioned musculo-elastic intimal thickening and hypertrophied media and adventitia at divisions of the main coronary arteries and also the myocardial branches. He considers these to be throttle arteries, with the function of regulating the blood flow through the end arteries of the heart. The medial hypertrophy he describes is in sharp contrast to the thinning found in the cases reported here. Arteries with these features are certainly rare in adult and infant hearts. I have examined routine sections of twenty-four infant hearts removed at consecutive autopsies, including twelve without heart disease and twelve with congenital heart disease, and have not found the features described by Zinck. The likelihood remains, therefore, that the intimal thickening seen in the cases described here can be considered abnormal, and the question poses itself as to why the changes are not seen more often.

Eakin and Abbott[45] reported a case of pulmonary conus stenosis with endocardial and myocardial fibrosis in which there was intimal thickening of the coronary arterioles in the area of fibrosis.

Thoma,[38] in his well-known experiment, found medial thinning distal to arterial ligation. However, the process did not extend into the smaller branches of the artery. It has not been demonstrated that diminished intraluminal pressure per se will cause the intimal and medial changes found in the two presented cases.

The possibility remains that these vascular changes represent a response to chronic anoxia of the vessel wall itself and that pathologic-anatomic and experimental studies may reveal similar changes and so help to establish the pathogenesis.

SUMMARY

1. Clinical and autopsy findings are reported in two infants, aged 3 and 6 months at death, in whom the left coronary artery arose from the pulmonary artery. No additional cardiac anomalies were present. The literature is reviewed.

2. In both cases there was excessive dilatation and hypertrophy of the left ventricle, with necrosis, fibrosis, calcification, and dilated sinuses in the myocardium. There was musculoelastic thickening of the intima of some of the smaller arteries. Fibroelastic thickening of the endocardium of the left ventricle was present. It is felt that these changes are atributable to chronic anoxia of the portion of the heart supplied by the left coronary artery.

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THE PLETHYSMOGRAPHIC MEASUREMENT OF BLOOD FLOW THROUGH THE FOREPAW DURING EXPERIMENTAL SHOCK

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EVIDENCE has accumulated that in experimental shock in animals there is an active peripheral vasoconstriction which greatly decreases the blood flow through peripheral vessels.[1-3] This has been considered to be the cause of a prolongation of the circulation time in this condition.[4] Similar reductions in the peripheral blood flow in the limbs of man have been reported. These reports were based on measurements with the venous occlusion plethysmograph[5-8] and on observations of the capillary bed of the fingernail.[9]

It was felt that determination of the time course of the blood flow changes in the periphery during the development of the shocklike state and their correlation with the simultaneously recorded blood pressure changes would help explain some of the changes seen in shock. For this purpose, a venous occlusion plethysmograph, based on the principles evolved by Landowne and Katz[10] for the larger plethysmograph applicable to man, was adapted for animal studies. The flow in a limb during the course of shock was determined by this means and the data were compared with the simultaneously recorded arterial blood pressure (obtained with the direct needle manometer of Hamilton and co-workers[11]).

Plethysmograph for Use in the Dog.—The volume of the dog's forepaw is so much smaller than the volume of the human hand, leg, or forearm that a more sensitive plethysmograph is required. After considerable trial, a plethysmograph was developed which was found adequate for our purpose. Sensitivity was increased and finer adjustment of sensitivity could be made by (1) a water bladder which permits control of the air space in the plethysmograph and (2) a modification of the Frommer pressure recorder developed in this laboratory.[12] As described previously,[12] this instrument records pressure changes by means of a condenser in which one plate is fixed, while the position of the other is changed by the pressure alterations impinging upon it. For the purpose of recording the very slight pressure rise produced in the plethysmograph chamber upon obstruction of the venous flow, the variable condenser of the Frommer apparatus

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was made very sensitive by mounting the movable metal plate on a thin airtight rubber membrane; electrical contact between the metal plate and the metal tube of the condenser was maintained by a thin wire bridge. The use of the Frommer apparatus also made it possible to record the pressure rises close to the plethysmograph since the condenser head could be placed next to it, while a long flexible cable served to connect the condenser to the amplifier. The assembled plethysmograph is shown in Fig. 1.

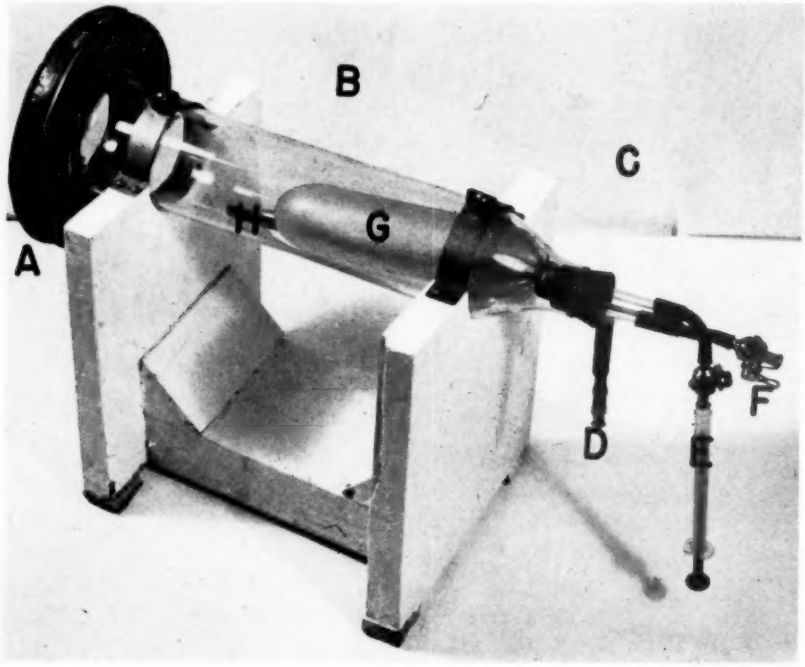

Fig. 1.—Larger glass plethysmograph assembled for use. *A* is the collar. *B* is the plethysmograph body (2¼ inches in diameter and 8 inches long); a smaller one (1¼ inches in diameter) was also used. *C* is the "tail." The plethysmograph consists of a 5-inch glass flange with heavy rubber tire inner tube glued to each side for cushioning effect; on the side of the flange toward the glass chamber, a metal plate is fastened to permit clamping of the metal plate diaphragm. *D* is the recording outlet connected to the Frommer recorder. *E* is a tuberculin syringe used for calibration; the stopcock above it is closed when not in use. *F* is the outlet to allow the pressure in the plethysmograph to reach atmospheric before a flow reading is taken; the stopcock is open except when a reading is being taken. *G* is the water-filled rubber bladder (a condom) employed to alter the air space in the plethysmograph for adjustment of sensitivity; this is accomplished by changing its size by adding or removing fluid through a fenestrated tube within the bladder. *H* is a perforated tube connected to the outlet for recording the pressure changes in the plethysmograph. The plethysmograph is constructed of glass so that the limb can be directly observed as to position, color, and state of superficial veins. In addition, it is possible to judge directly the amount of air space and the placement of the bladder, *G*. The latter is important in order to avoid direct contact between the bladder and forepaw. See text for further discussion.

PROCEDURE

The dog was anesthetized with nembutal (25 mg. per kilogram of body weight) and the left forepaw carefully shaved. A square of dental rubber dam was cut with a central hole 2 or 3 mm. smaller than the diameter of the paw

below the sixth callosity, which is above the humero-ulnar joint on the inner aspect of the paw. A layer of rubber cement was applied to a narrow strip of skin and to the surface of a brass plate with an opening of sufficient size to permit passage of the forepaw. The rubber diaphragm was cemented to the brass plate and both pulled over the paw to make an airtight seal on the cemented skin just distal to the sixth callosity.

The forepaw was inserted into the plethysmograph chamber and the brass ring clamped to the collar of the plethysmograph; lubricant jelly was used as a seal. The volume of paw inserted in the chamber was determined by measuring the amount of water used to fill the chamber and subtracting the value from the capacity of the chamber. Enough water was left in the chamber after draining to assure water vapor saturation. After draining off the water, the rubber bladder and the parts for recording were inserted in the opposite end of the chamber. The rubber bladder was filled with water at room temperature, the condenser head of the Frommer apparatus attached to the air outlet of the plethysmograph, and the apparatus checked for leaks. Leaks were tested for by the ability of the plethysmograph to hold pressure when small amounts of water were added to the bladder.

The venous occlusion cuff was next wound around the paw just proximal to the sixth callosity and the arterial occlusion cuff, just distal to the humero-ulnar joint. This was arranged so that it could be quickly connected to a large air pressure reservoir at the desired level. The Hamilton manometer was connected to a cannula in the left common carotid artery. All the tubes were connected, the electrical circuits closed, the recording lights turned on, and the camera started.

Next, a test for "tissue bulge artefact" was made by inflating the arterial cuff above the systolic arterial pressure (usually to about 250 mm. Hg) and then inflating the venous occlusion cuff to about 60 to 70 mm. Hg. Any shift in the plethysmographic volume observed under these conditions can only be due to movements of tissue in or out of the plethysmograph. Readjustments of the degrees of flexion and extension of the paw usually eliminated or minimized this artefact as well as the movements of the paw in and out of the plethysmograph during respiration.

Calibration of the plethysmograph was repeated before practically every record of blood flow. This was accomplished by injecting a known quantity of water into the water bladder of the plethysmograph and recording the change in pressure level.

Four to six control flow readings were obtained before injection of lampblack into the veins of both hind limbs. The technique for the latter operation was that described previously.[13] Readings were repeated at five-minute intervals postoperatively until flow was minimal or appeared to be zero. Thereafter flow readings were taken at thirty- to sixty-minute intervals until the death of the animal. A total of five such dogs were studied. Controls were run on four other dogs who were maintained under anesthesia for a number of hours without the lampblack injection; two of these were subjected to a laparotomy and dissection of the common iliac vein.

Precautions in the Use of the Plethysmograph and Pitfalls in Its Use.—Pitfalls which can ordinarily be avoided include the following:

1. Leaks in the apparatus. These may result from a rubber diaphragm with an opening too large for the paw. Great care must be used in shaving the forepaw to avoid abrasion or skin cut which prevents the rubber cement from adhering to the skin.

2. Movements of the limb into or out of the plethysmograph (Fig. 2, *A* and *B*). These will cause movements of the base line. Extremely slow movements are not per se disturbing since the plethysmograph air outlet can be opened to bring the pressure back to atmospheric. Such slow base line movements, however, may represent changes in the quantity of blood within the forepaw. A steady increase may occur with venous engorgement when the opening in the rubber diaphragm is too tight; it is to be avoided. More rapid movements of the base line may represent respiratory artefacts or be due to too light anesthesia

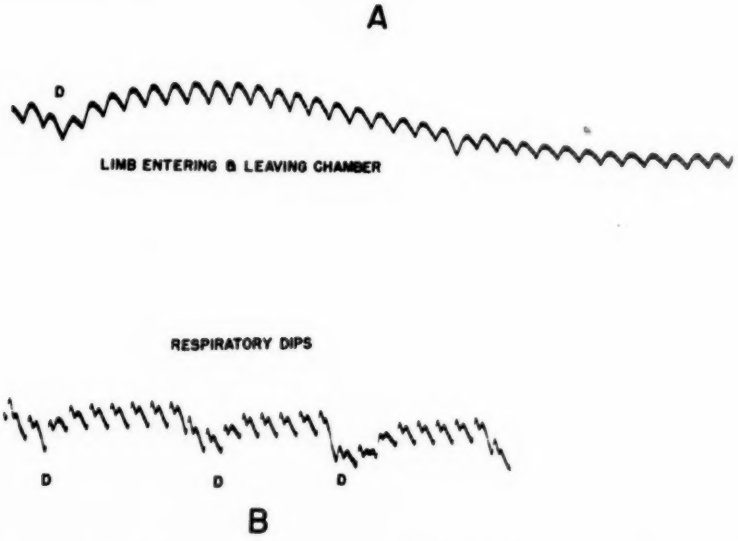

Fig. 2.—Several types of artefacts encountered with the plethysmograph. In *A*, a shift of the record is seen due to respiratory movement of the limb in and out of the plethysmograph (the rise and fall, respectively); superimposed on this is the volume pulse and two dips also due to respiration, the first labelled *D*. In *B* there is seen, besides the volume pulse, a number of dips, *D*, due to respiration; in addition, a slower downward movement of the record is present, suggesting a nonrespiratory movement of the limb out of the plethysmograph. See text for further discussion.

or poor fastening of the paw in the chamber. This can be remedied by altering the angle of flexion of the forepaw, by shifting the angle of flexion of the entire leg, by fixing the humero-ulnar joint, or by increasing the depth of anesthesia.

3. Venous occlusion artefact. This was discussed in the foregoing. In the course of an experiment it was found to lessen as the animal went into shock.

It is obvious that as the arterial pressure falls with the development of shock, the pressure used to inflate the venous cuff must be diminished in order to keep

it well below the diastolic pressure, since otherwise the inflow will be reduced and a false low reading obtained.

Recording the Blood Flow and Analysis of the Record.—The blood flow was obtained from the change in pressure in the plethysmograph chamber recorded on the photokymograph. A typical record is shown in Fig. 3. Records were checked for the presence of artefacts as discussed in the preceding section. Where present, this portion of the record was not used for reading. Excluding records with artefacts, all readings were taken during the second in which the blood flow was maximal. The vertical displacement of the pressure curve during this

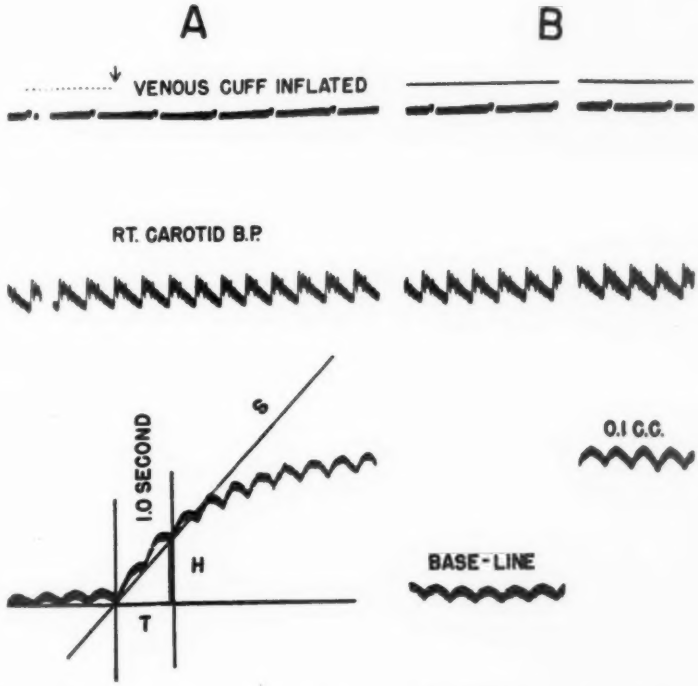

Fig. 3.—A typical record (without artefacts) for calculation of flow. In *A* is shown the record before and after venous occlusion marked by an arrow in the top line. The records from above down are: the record of the signal magnet which signals time of venous occlusion, time line in seconds, right carotid intra-arterial pressure curve, forepaw blood flow record. On the lower curve, the method of calculating flow is shown. *S* is the slope of the volume increase, *T* is the time interval of 1.0 second on the base line, *H* is the vertical height attained by *S* in 1 second. The calibration record is shown in *B;* the difference in height of the volume record in the two portions represents 0.1 c.c. See text for further discussion.

second was measured off, using homologous points of the successive pulses, and expressed as a multiple of the vertical distance between two successive calibration lines. Temperature and barometric pressure data showed small enough fluctuations to be negligible. Flow readings were converted to cubic centimeters per minute per 100 c.c. limb volume.

Several errors in reading flows from the pressure record were encountered. These are pointed out to show that the method is not as precise as desirable, a defect which this plethysmograph shares with others.

The calibration lines were found to show (1) greatly variable distances in successive calibrations, (2) at times, oscillations instead of a steady horizontal line, (3) more commonly an upward or downward slant, and (4) different increments in height for each successive tenth of 1.0 c.c. of water added. The last is due to the different sensitivity of the membrane in the different pressure regions. It need not introduce an error if the calibration distance used for conversion is chosen at the level of the portion of the record used for reading. The other disturbances were encountered much more frequently and to much greater degree before the animal went into shock. They are, therefore, probably due to tissue movement in and out of the chamber. A contributing factor to the variability of successive calibrations may be the inaccuracy of measuring 0.1 and 0.05 c.c. quantities with a tuberculin syringe. Of greater importance seems the fact that the camera was turned on after the fluid was introduced and the stopcock between syringe and water bladder closed. Tissue movement in this time interval would not be on record, yet may have caused a shift of the pressure line by the time recording started. Thus the second half of a respiratory dip might appear as an upward slant. To avoid biased reading of the records, the first portion of the calibration line was arbitrarily considered as determining the distance in all cases, since it was usually not possible to state which was the calibration level and which were the accidental deviations from it.

Another error is due to the fact that not all of the paw occluded was within the plethysmograph. The plethysmograph was below the sixth callosity and the venous cuff above it (0.5 to 1.0 cm. proximal to the collar of the cuff). Under such circumstances it is possible that redistribution of blood between the intra- and extraplethysmographic portions of the paw would change the slopes.

It is apparent that the flow determinations, especially in animals not in shock, are crude and have a large experimental error. Actual successive determinations of four to six readings three to five minutes apart showed an average variation of 31 per cent (standard deviation, 25.2) in eleven anesthetized dogs. Doubtless some of the variation was real, but much of it was due to the experimental error of the measurement. Successive determinations in animals in a state of shock usually showed very good agreement, and, of course, it was possible to determine accurately the time at which no flow could be recorded.

RESULTS

Five dogs were studied in which bilateral venous occlusion led to a shock-like state with death in 5¼, 7¼, 8¼, 8½, and 14¾ hours. A typical experiment is shown in Fig. 4. It will be seen that the forepaw flow fell close to zero quickly within one and one-half hours, while the major fall in blood pressure and the rise in heart rate occurred later. This was representative of the four other experiments. The forepaw flow became imperceptible within one-fourth to one and three-fourths hours and to less than 1 per cent of the control flow (100

per cent being the average of four to six readings preceding the operation) within five to fifty minutes. Thus, it will be seen that the decrease in limb flow is rapid indeed. No correlation could be made between the time of survival of these dogs and the time course of the decline in forepaw blood flow.

The drop in blood pressure was more gradual. In the first hour it fell, on the average, 10 per cent below the control (even though values above control levels were observed in some dogs). This rate of fall was maintained for the next hour or two, with some acceleration of the rate depending on the rapidity with which shock became irreversible. In the last few hours of life the blood pressure dropped more and more rapidly, the heart rate accelerated greatly, and the pulse pressure declined. In the final hour these changes of blood pressure were associated with a progressive slowing of the pulse.

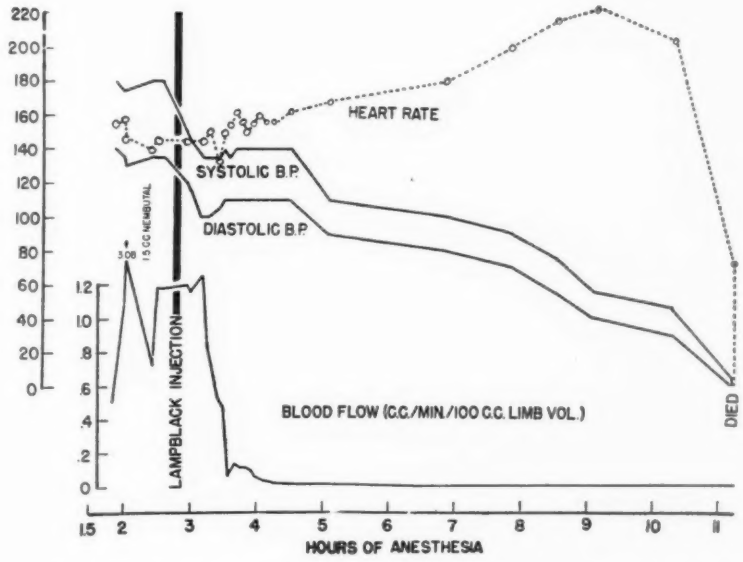

Fig. 4.—A typical experiment showing the effect of bilateral venous occlusion of the hind limbs upon the blood flow of the forepaw, the arterial blood pressure, and the heart rate. Abscissae represent hours after anesthesia was begun. The time of operation is indicated by the vertical block labelled lampblack injection. The various curves are labelled. Blood pressure is measured in millimeters of mercury; heart rate, in beats per minute. See text for further discussion.

Control studies were made on two dogs to determine the effect of protracted nembutal anesthesia. One of the experiments is shown in Fig. 5. It shows the wide variability in forepaw flow and the smaller fluctuation in blood pressure, but there was no discernible trend in the course of the experiments. Only the heart rate showed a progressive fall with time, due to the repeated injections of nembutal necessary to keep the animal immobile. Because of the progressive state of shock, it was not necessary to repeat the anesthesia in the experimental shock animals. It would appear, therefore, that the changes observed in venous occlusion shock are not due to the anesthesia employed.

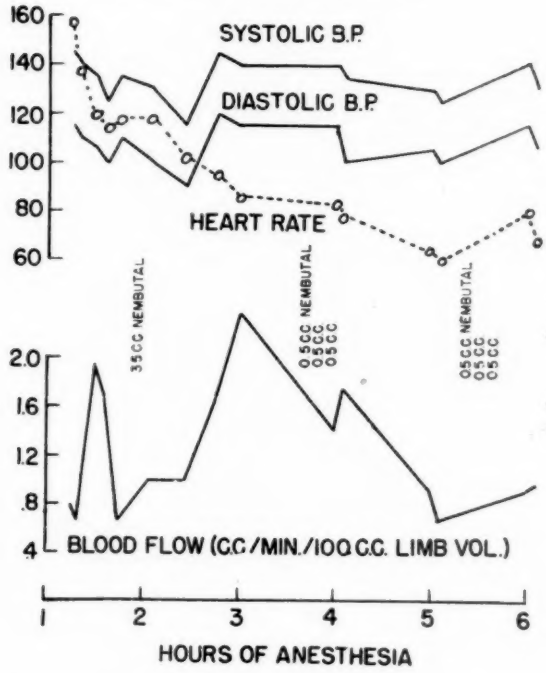

Fig. 5.—Control experiment in which the dog was kept anesthetized for six hours without other intervention. The initial dose of nembutal was 25 mg. per kilogram. Observations were begun one hour later. Abscissae represent hours after start of anesthesia. Ordinates as in Fig. 4. The time and quantity of further nembutal administration in indicated above the blood flow curve. See text for further discussion.

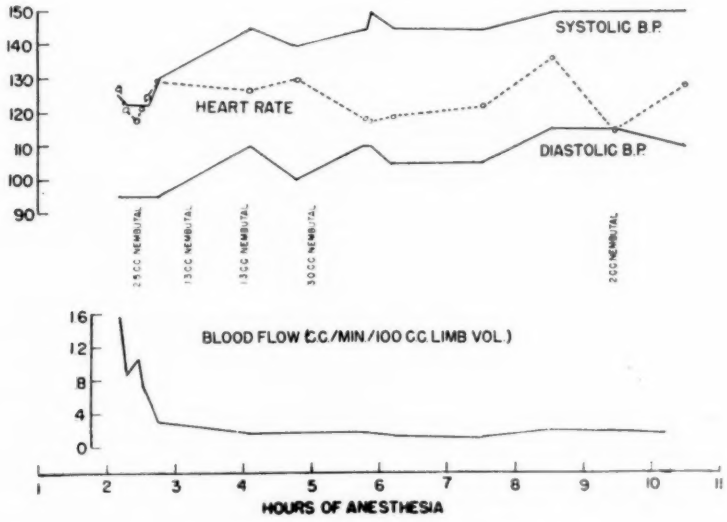

Fig. 6.—Control experiment in which the dog was kept anesthetized for eleven hours and in which a mock operation was performed just before the observations recorded in the figure. Conventions as in Figs. 4 and 5. See text for further discussion.

A second type of control was run on two dogs in which anesthesia was combined with a bilaterial mock operation identical with the experimental one, but omitting ligation of veins and injection of lampblack. The observations made in one of these dogs are shown in Fig. 6. Blood flow in the forepaw declined at much the same rate as in the shock animal but remained somewhat more than 12 per cent of the control flow. The blood pressure did not drop and the heart rate remained fairly uniform. The surgical procedure obviously had a marked effect on forepaw flow but it led neither to a progressive blood pressure or heart rate change nor to an apparent complete cessation of flow. Furthermore, these animals survived beyond the period during which the experimental animals succumbed.

It is interesting to note that one animal which survived the bilateral vein occlusion showed an early drop to a near-zero flow in the forepaw. For the ten hours of observation the flow did not appear to be resumed. In this animal the blood pressure fell at first, but toward the end of the period of observation it began to rise again toward normal while the blood flow was still close to zero. The observations on this animal and on the animals with mock operations probably depict the course of events in reversible shock and in the earliest stages of shock, respectively.

DISCUSSION

Blood flow in the forepaw, which is mainly skin flow, declines very early in a condition leading to shock. A distinction is to be made between a drop in forepaw flow and apparent cessation of forepaw flow. The former occurred even in conditions such as a simple laparotomy which did not lead to blood pressure drop or other evidence of shock. Reduction of flow may thus indicate impending shock but is not a sure sign of it. Apparent zero flow in the forepaw can be considered a sign of shock, but it is not a sign of irreversible shock, as evidenced by the long-continued apparent zero flow of the forepaw, associated with a delayed drop in blood pressure, in one animal which later recovered. The first evidence of this recovery was the return of blood pressure toward normal.

Our results are in accord with the now generally recognized view that blood flow in shock in general declines before the blood pressure[14,15] and that skin flow in particular declines to extremely low levels. Cardiac output, as indicated by heart size, begins to decrease at about the time that skin flow has apparently declined to zero.[13] Apparently, as the amount of circulating blood declines, blood is diverted from the less vital organs to those like heart and central nervous system (respiratory center) which must continue to function if the animal is to survive.

Thus it would appear that the decrease in peripheral flow, surely in skin flow, is a compensatory mechanism. That the skin flow appears to reach zero so early in shock means that the compensatory vasoconstriction in this region is brought into play very quickly and to its utmost extent.

Tachycardia develops much later than the drop in skin flow and is progressive, while the drop in skin flow is early and apparently complete. Since both the skin vasoconstriction and the tachycardia are doubtless chiefly reflex in origin, it is of interest that the timing and pattern of these two phenomena are so different.

If these results can be applied to man, a pale and cold skin, the sign of skin vasoconstriction in man, should be viewed as an *early* sign of impending shock (obviously a pale cold skin occurs in other circumstances).

Our results also suggest an explanation for the detrimental effect of heat application reported in shock.[16] If the reduction of skin flow close to zero is a compensatory mechanism in shock, then heat applied to the body should be avoided for it would lead to release of the vasoconstriction and divert blood from more vital organs to the skin.

SUMMARY

1. The skin flow of the forepaw of the dog was studied in a standardized type of experimental shock (following venous occlusion of the hind limb).

2. A small animal plethysmograph used for this purpose is analyzed.

3. The results indicate that the blood flow in the forepaw apparently falls to zero very early in the development of the shocklike state. Furthermore, this drop in blood flow occurs much earlier than the fall in blood pressure or the increase in heart rate.

4. Anesthesia per se does not affect the blood flow. Mock operations reduce the blood flow but do not suppress it.

5. A physiologic correlation between the peripheral blood flow, arterial blood pressure, and heart rate in the development of the shocklike state is discussed.

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ON THE MECHANISM OF PAROXYSMAL TACHYCARDIA WITH RHYTHMIC ALTERNATION IN THE DIRECTION OF THE VENTRICULAR COMPLEXES

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PAROXYSMAL ventricular tachycardia is uncommon, although with the increasing number of electrocardiograms being taken, it is now being detected more frequently. The so-called bidirectional type, or paroxysmal ventricular tachycardia with rhythmic alternation in direction of the ventricular complexes, is even more uncommon. In the past thirty years at the Rhode Island Hospital electrocardiograms have been obtained in twenty-eight patients with paroxysmal ventricular tachycardia. Only one of these has shown the bidirectional type. This case is reported because of the interesting clinical and electrocardiographic findings which bear on the underlying mechanism. The discussion will be limited to the bidirectional alternating type of ventricular tachycardia.

REVIEW OF THE LITERATURE

In 1911, Levy and Lewis,[1] working on cats which were exposed to low tension chloroform vapor, produced an irregular tachycardia caused by ventricular extrasystoles which were thought to originate in multiple foci. From time to time they obtained tracings showing a ventricular tachycardia in which the complexes alternated in direction. They felt that this configuration was the result of premature contractions alternately generated in separate foci. Small intravenous injections of adrenaline chloride given to cats under the influence of low tension chloroform vapor caused these irregularities to progress ultimately into ventricular fibrillation.

The first example of regular alternation of upward and downward deflections in man was published by Schwensen[2] in 1922. He reported on two patients with ventricular tachycardia, both of whom had received digitalis. The first showed coupling due to ventricular extrasystoles and the second patient, who had rheumatic heart disease with auricular fibrillation, showed paroxysms of bidirectional ventricular tachycardia. Schwensen discussed the possibility of this being due to hyperirritability of the ventricle resulting from the administration of digitalis.

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Similar cases were subsequently reported by Felberbaum,[3] Reid,[4] Luten,[5] Clerc and Levy,[21] Marvin,[9] Clarke,[12] Schwab,[15] Howard,[16] and Piloni,[17] in all of which digitalis was thought to play an important etiologic role.

Sherf and Kisch[18] reported their observations of eighteen cases of paroxysmal ventricular tachycardia which they divided into three types: (1) ventricular tachycardia with regular rhythm and the alternation of two kinds of ventricular complexes (Type I); (2) ventricular tachycardia with an alternation of two types of ventricular complexes and an alternation of a longer and shorter diastole (Type II); (3) ventricular tachycardia in which the shape of the ventricular complexes as well as the length of diastole changed irregularly (Type III). Three of their patients on whom data were published showed the typical alternating bidirectional ventricular complexes. Fourteen of their eighteen patients were receiving digitalis when the tachycardia appeared. They concluded that the quantity of digitalis administered is not a factor of exclusive importance and that the condition of the myocardium is a more important factor.

Recently, Braun and Wosika[19] reported another case in a 68-year-old man with auricular fibrillation and congestive failure. On two occasions this patient developed bidirectional ventricular tachycardia following the use of *Digitalis purpurea*. Strophanthin and *Digitalis lanata* produced no toxic effects. The patient was improved on discharge from the hospital.

Gilchrist[7] reported five cases of paroxysmal ventricular tachycardia. In one patient (Case 4) a rhythmic alternation in direction of complexes was seen for a few cycles at the beginning of the record. Nicotine intoxication was regarded as important in the production of the arrythmia in this particular patient.

Orsi and Villa[10] reported on one patient in whom a change from the usual type of ventricular tachycardia to the alternating bidirectional form occurred a few seconds following the intravenous injection of calcium chloride.

Additional cases have been reported by Smith,[11] Strauss,[13] Langeron,[14] Gallavardin,[6] and Palmer and White.[8] Howard[20] reviewed the tachycardias due to digitalis without adding any new case of the bidirectional alternating type.

Several theories have been advanced to explain the phenomenon of the alternating complexes of ventricular tachycardia. Two possibilities were recognized by Schwensen,[2] Felberbaum,[3] and Luten.[5] One was that the origin of the impulses was in a single focus above the bifurcation of the bundle of His and the alternating direction was the result of alternating conduction through the right and left bundle branches. The second was that the impulses originated within the ventricles and that they were generated alternately in the right and left chambers.

Gallavardin[6] was the first to suggest the possibility of circus movement in the ventricles as an explanation for this unusual type of tachycardia. Palmer and White[8] rejected the explanation that all ventricular impulses arose in one focus located above the bundle of His, because they found an alternation of the length of diastole in two of their patients. After discussing such possible mechanisms as parasystole and re-entry, these authors suggested that the phenomenon was due to a double ventricular circus movement.

Howard[16] suggested that "The mechanism depends upon a relatively fixed delay in conduction time of one branch of the bundle, while the conductivity of the other branch waxes and wanes so that it alternately exceeds and fails to equal that of the first branch."

Scherf and Kisch[18] attempted to show that in every one of their three types, a single center of stimulus formation may exist, while the abnormal picture may be caused simply by a disturbance of intraventricular conduction. Braun and Wosika[19] concluded that "The assumption that multiple ectopic foci are present in the damaged myocardium and are responsible for this alternating paroxysmal tachycardia cannot be avoided. The height of the paroxysm may be the result of interference phenomena, or of the predominance of two centers of the same order over the other ectopic foci."

Summary.—Including the case to be discussed herewith, thirty-two cases have been reported in which alternating bidirectional ventricular tachycardia has been observed. These include instances of continuous alternation in the direction of the complexes and instances in which only brief groups of alternating bidirectional ventricular complexes were recorded.

Of these thirty-two patients, twenty-six died soon after the arrhythmia was discovered, one lived twenty-five days after its onset, our patient lived seventy-two days after its onset, and one patient lived five months after the disturbance first appeared. The patient reported by Braun and Wosika was still living twenty-seven months after the attack of alternating bidirectional ventricular tachycardia. One patient was improved on discharge and one returned to work but could not be traced subsequently.

Excluding three of Gallavardin's patients in whom it is uncertain whether digitalis was administered, all but two of the patients received digitalis. The patient reported on by Orsi and Villa showed alternating bidirectional ventricular tachycardia a few seconds following an intravenous injection of calcium chloride. The patient previously had received ouabain intravenously. In one patient, nicotine intoxication was thought to be the exciting factor.

CASE REPORT

W. S., a 57-year-old man of Italian descent, was admitted to the Rhode Island Hospital Oct. 7, 1945.

Present Illness.—The patient had known that he had hypertension for several years. Cardiac symptoms had been present for about eighteen months. Seven months before admission he had become extremely weak, short of breath, and unable to continue his work. He was given digitalis and continued to take a maintenance dose of 0.1 Gm. daily. He had occasional severe attacks of dyspnea and at such times he increased the digitalis dosage to 0.2 or 0.3 Gm. daily. He became progressively worse and his attending physician sent him to the hospital. The past medical history, family history, and review of the systems were irrelevant.

Physical Examination.—The temperature was 101.0° F.; pulse rate, 130; and respiratory rate, 32 per minute. The patient was in severe congestive failure with dyspnea, orthopnea, and generalized anasarca. The cardiac rhythm was regular with occasional extrasystoles. The maximum apical impulse was 2.5 cm. to the left of the midclavicular line. There were no murmurs. The blood pressure was 200/110.

It was noted that paroxysms of tachycardia were occurring intermittently. At such times the heart rate was very rapid and regular and the patient complained of palpitation. Carotid sinus pressure terminated these attacks immediately. An electrocardiogram, taken in the morning of Oct. 8, 1945 (Fig. 2), showed the paroxysms to consist of bidirectional, alternating ventricular tachycardia, which was recorded in several tracings. A thoracentesis was performed and 1,225

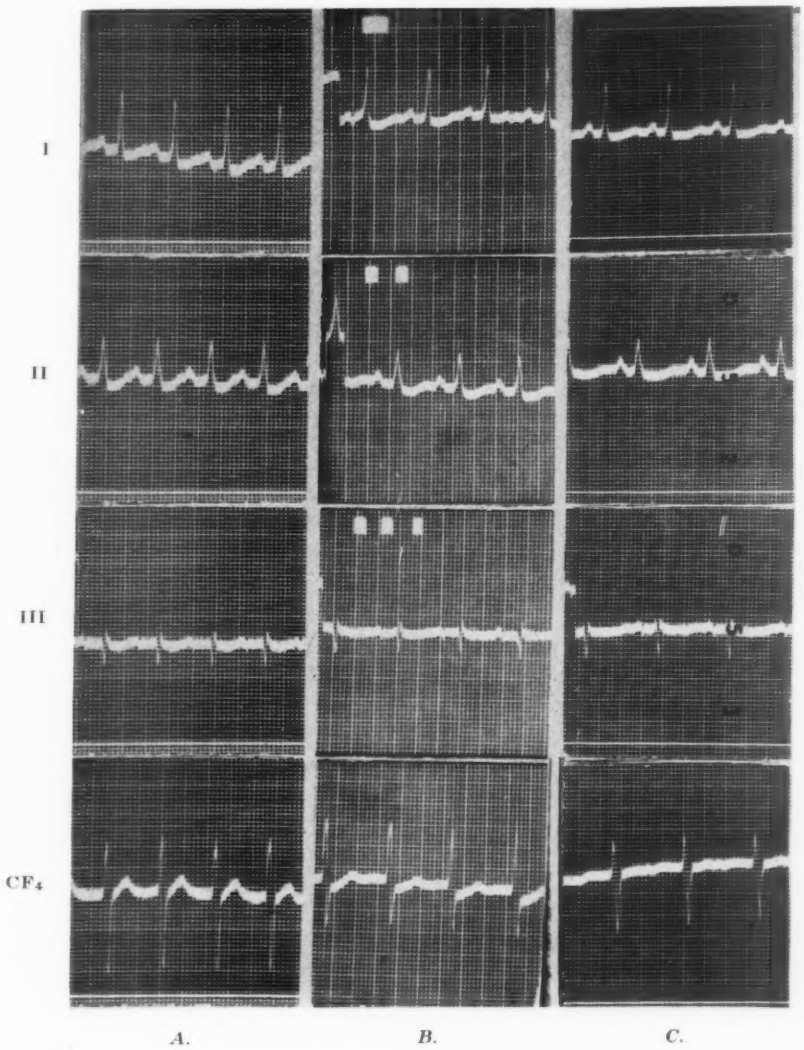

Fig. 1.—Leads I, II, III, and CF_4. *A*, Electrocardiogram taken before admission. B, A tracing taken October 9. *C*, A record taken November 13. Later tracings showed no changes.

c.c. of clear fluid was obtained. Following this, an electrocardiogram, taken in the afternoon of Oct. 8, 1945 (Fig. 5), differed considerably from the one taken in the morning. Auricular fibrillation was present together with a marked degree of A-V block and an idioventricular rhythm. On Oct. 9, 1945, an electrocardiogram (Fig. 1, *B*) showed a regular sinus rhythm with a rate of

109 per minute. He had no further episodes of tachycardia that were noted clinically while in the hospital.

Laboratory Studies.—The blood urea nitrogen was 20 mg. per cent; blood sugar, 102 mg. per cent; and blood cholesterol, 208 mg. per cent. Urinalysis showed a specific gravity of 1.007 with a 1 plus protein. Blood examination showed erythrocytes, 5,580,000; white blood cells, 10,150, and hemoglobin, 12.4 grams. Differential count was 84 per cent neutrophiles, 12 per cent lymphocytes, and 4 per cent monocytes.

Diagnosis.—The diagnosis was arteriosclerotic and hypertensive cardiovascular disease, cardiac decompensation, bilateral hydrothorax, and bidirectional alternating ventricular tachycardia.

Clinical Course.—After the first thoracentesis, the patient was placed in an oxygen tent where he was less dyspneic. He was given 0.2 Gm. of quinidine sulfate four times daily. Ammonium chloride and mercupurin were also administered with good effects. A second thoracentesis was performed October 15 and 800 c.c. of fluid obtained. On October 26, 490 c.c. of fluid was removed. With this therapy, the patient improved slowly and the edema diminished. Digitalis was discontinued on admission.

On Nov. 17, 1945, the patient sat up in a chair and felt much stronger. The heart rhythm was regular and the rate varied between 84 and 90 per minute. The blood pressure was 140/90.

An electrocardiogram taken Nov. 13, 1945 (Fig. 1, *C*) showed normal sinus rhythm with a rate of 86 per minute. The conduction time was slightly increased. The P waves were prominent in Leads I and II. The T waves in Lead IV were still small. The S-T intervals were slightly depressed in Leads I and II.

On Nov. 19, 1945, the patient returned to his home where treatment included quinidine sulfate, four times daily. He remained in bed but his condition became progressively worse. He died thirty-two days after discharge from the hospital. No autopsy was performed.

DISCUSSION

The appearance of regular alternation in the direction of the complexes in ventricular tachycardia has been associated with severe cardiac damage and pathologic changes in the heart. The prognosis is usually very poor.

In the total series of thirty-two patients, excluding the patient of Clerc and Levy[21] because the case report was not clear, the diagnoses were as follows: Arteriosclerotic heart disease with aortic stenosis, 1; arteriosclerotic and hypertensive heart disease, 9; coronary thrombosis, 2; chronic myocarditis, 2; coronary sclerosis without hypertension, 4; syphilitic heart disease, 5; rheumatic heart disease, 4; uremia, 1; tuberculous myocarditis, 1; cardiac enlargement of unknown etiology, 1; and no heart disease, 1.

Cardiac asthma occurred in four patients, anginal failure in one, and congestive failure in twenty-six. Auricular fibrillation was observed in fifteen of the thirty-one patients.

The age distribution was 16 to 80 years and averaged 55.9 years. There were eleven women and twenty men in the series.

In none of the reported cases has it been possible to prove convincingly which type of mechanism is responsible. We wish to offer an explanation of the mechanism of the peculiar type of ventricular tachycardia which occurred in our patient. We believe that both clinical and electrocardiographic evidence indicate that there were two separate foci functioning, one in the supraventricular A-V nodal tissue and the other in the ventricles.

In this patient, every episode of tachycardia could be terminated abruptly by carotid sinus pressure. The tachycardia was demonstrated by the electrocardiograms to be the type designated as bidirectional alternating ventricular tachycardia. Pressure over the carotid sinus on either side was equally effective. A record of the effect is shown in Fig. 4.

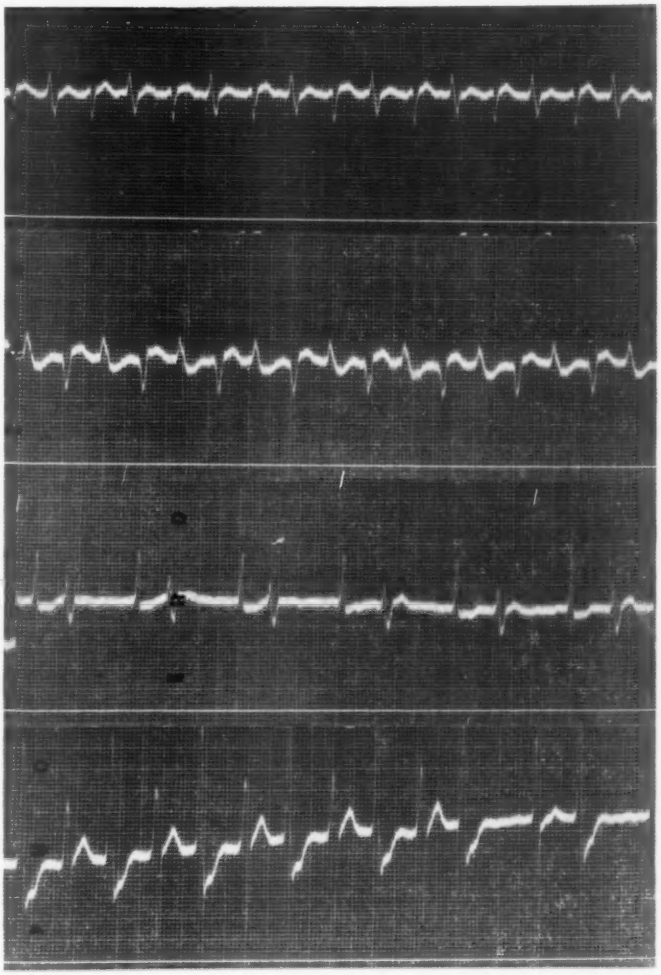

Fig. 2.—Leads I, II, III, and CF_4. Bidirectional alternating tachycardia. The interval following the upright complex is longer by 0.04 second than the interval between the downward complex and next upright complex. Lead III shows coupled rhythm following carotid sinus pressure.

It is known that increased vagal tone will stop supraventricular tachycardia, but it is thought that such stimulation has no effect upon ventricular tachycardia. Fibers from the right vagus nerve terminate around ganglion cells in auricular tissue in the immediate neighborhood of the sinoauricular node. The left vagus nerve establishes a similar relationship with the auriculoventricular node.

In mammals the vagus nerves exert their effect upon the heart through their action on the auricular muscle and the junctional tissues. They exert no direct effect upon the ventricular muscle. If the A-V bundle is severed, vagal stimulation is then without effect upon the ventricular rate.[23]

Fig. 1 shows electrocardiograms taken on several occasions. *A*, a tracing taken before hospital admission, shows regular sinus rhythm with a P-R interval of 0.20 second. The S-T intervals in Leads I and II are depressed. The T waves are small and diphasic in the limb leads and upright in Lead CF_4: Left axis deviation is present. *B* shows a record taken October 9. It is quite similar to the previous one, except that the S-T segments in Lead CF_4 are depressed. *C* shows a record taken November 13. The rate is slower. The P waves are prominent in Leads I and II. The T waves in Lead CF_4 are smaller and the S-T segment is isoelectric.

Fig. 2 shows the bidirectional alternating ventricular tachycardia. The interval following the upright complex is longer by 0.04 second than the interval between the downward complex and the next upright complex. Smith[11] found the same to be true in his patient. Palmer and White[8] found the interval following the inverted complexes to be longer than that occurring after the upright complexes. Lead III was taken following carotid sinus pressure. It shows coupled rhythm.

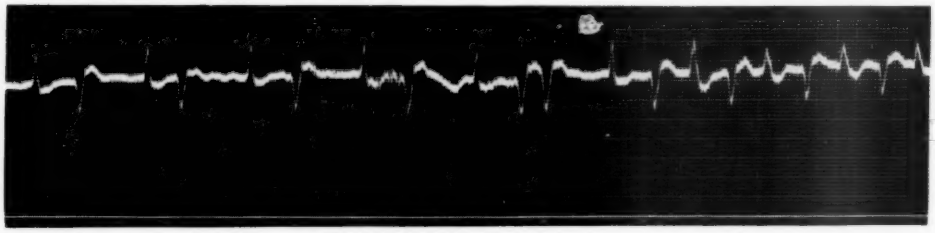

Fig. 3.—Lead II. The beginning of a paroxysm of bidirectional alternating tachycardia. Description in text.

Fig. 3 shows the beginning of one of the patient's paroxysms of bidirectional alternating ventricular tachycardia (Lead II). In the first part of the strip there is a coupled rhythm produced by ventricular extrasystoles. The deflection time increases from 0.07 to 0.10 second in the upward-directed beats of the tachycardia.

Fig. 4 (Lead III) shows the ending by carotid sinus pressure of the bidirectional alternating tachycardia. Carotid sinus pressure is indicated by *X*. This is followed by two downward deflected complexes in succession and establishment of a rhythm in which no auricular waves are seen. In the bottom strip this rhythm is quite regular. The extrasystoles in the coupled rhythm very closely resemble the complexes in the tachycardia that are directed downward. Carotid sinus pressure abolished the upward complexes which must have originated in the nodal tissues. The auricular pacemaker then resumed its function, while the

ectopic foci in the ventricles still exerted themselves at times. In some instances these ventricular beats follow the dominant beats at a fixed interval and in other instances they occur at different times during the cycle.

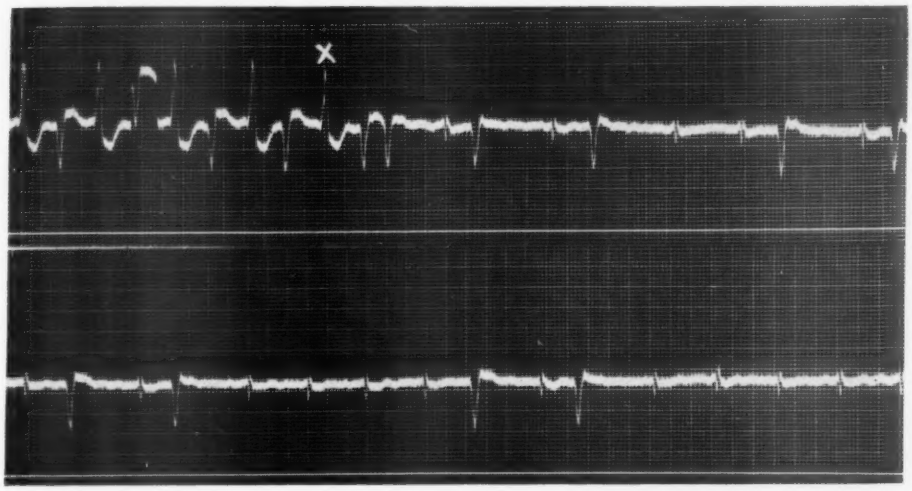

Fig. 4.—Lead III. The ending by carotid sinus pressure of the rhythmic alternation in the direction of the ventricular complexes. Carotid sinus pressure is indicated by *X*.

Fig. 5 is a continuous record of Lead II taken between the patient's attacks of bidirectional alternating tachycardia. It shows auricular fibrillation with complete A-V heart block. In the first strip, at the beginning, the rate of the ventricles is 100. This slows to about 93 per minute. In the second and third strips there are frequent extrasystoles appearing in different parts of the cycle. Since the QRS complex is normal in duration, the idioventricular rhythm apparently arises in the A-V node. A similar tracing has been published by Katz.[22]

Most of the reported cases have been associated with digitalis and some of the patients received toxic doses of digitalis. It is known that digitalis acts on the junctional tissue to slow conductivity. It is also known that digitalis causes ventricular ectopic beats as an early manifestation of intoxication and the ectopic beats may be increased in frequency until regular coupled rhythm is produced by continued administration of the drug.

Marvin[9] stated that in his patient, "careful consideration of the doses and circumstances in which they were used leaves the impression that there are probably factors other than the total amount of digitalis which may be responsible for the onset of the mechanism under discussion." Schwab[15] concluded that the role of digitalis as an exciting factor in the causation of ventricular tachycardia was much more apparent after a study of the reported cases of the alternating type. Especially of interest is the patient reported on by Braun and Wosika[19] in whom *Digitalis purpurea* brought on attacks of bidirectional ventricular tachycardia. These disappeared after strophanthin and *Digitalis lanata* were substituted. Digitalis may act in these patients with already damaged tissues to

depress the conduction system until a nodal pacemaker suddenly takes over. It is also of interest to observe that many of the reported cases were associated with auricular fibrillation and periods of coupling before the abnormal rhythm occurred. In Fig. 3 is shown the transition from the bigeminal rhythm into the bidirectional tachycardia in our patient. It is conceivable that digitalis causes a high degree of A-V block in reported patients, leaving some part of the nodal tissue suddenly to assume control along with an ectopic focus in the ventricles and produce this abnormal pattern of bidirectional alternating tachycardia. Though this is purely speculative, we do believe that the mechanism of production causing the arrhythmia in our patient is clear. Because of the instant remarkable re-

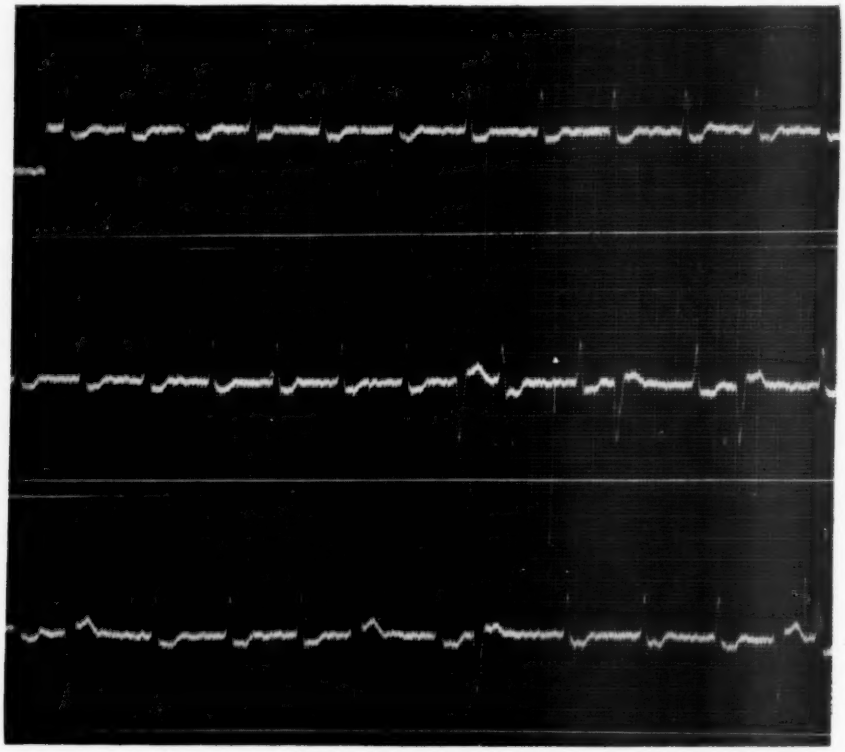

Fig. 5.—Lead II. Portions of a continuous tracing taken between the patient's attacks of alternating bidirectional tachycardia. Description in text.

sponse to carotid sinus stimulation with the resultant electrocardiographic findings, it is evident that there were two foci functioning, one in the tissues responsive to vagus stimulation and the other in tissues not responsive. We believe, therefore, that in our patient there were two distinct sites from which the impulses originated: one in the bundle of His above the bifurcation of the bundle and the other in an ectopic focus in the ventricles. If our observations are correct, we also suggest that this arrhythmia be described not as paroxysmal bidirectional ventricular tachycardia, but as paroxysmal tachycardia with rhythmic alternation in the direction of the ventricular complexes.

SUMMARY

1. A case of paroxysmal tachycardia with rhythmic alternation in the direction of the ventricular complexes in the electrocardiogram is reported together with a review of the literature.

2. There have been thirty-two cases of bidirectional alternating ventricular tachycardia recorded in the literature, most of these associated with severe cardiac damage and digitalis administration.

3. We have presented clinical and electrocardiographic evidence which suggests that in our patient the mechanism was due to the action of two separate foci, one in the A-V nodal tissues above the bifurcation of the bundle of His the other in the ventricular muscle.

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THE HEART IN ACUTE ANTERIOR POLIOMYELITIS

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THE occurrence of acute myocarditis incident to severe infection is classically exemplified in rheumatic fever and in diphtheria. Certain viral infections, including mumps[1] and influenza,[2] have been incriminated rarely as a cause of acute myocarditis. Saphir and Wile[3] demonstrated the presence of focal perivascular and diffuse interstitial cellular invasion in the heart in six of seven fatal cases of poliomyelitis. Myocarditis was not suspected clinically in any of these patients, although, in retrospect, suggestive features were present: rapid, feeble pulse, diminished blood pressure, tachycardia out of proportion to the temperature, and cyanosis. Peale and Lucchesi[4] found microscopic evidence of myocarditis in five of seven fatal cases of poliomyelitis. The changes consisted of vascular, perivascular, and interstitial cellular infiltration. Myocarditis had not been considered before the death of these patients.

The undeniable presence of acute myocardial changes in a high percentage of fatal cases of poliomyelitis suggested to us the advisability of careful cardiac studies in patients suffering from this disease. Our report is based upon the evaluation of 467 patients with acute poliomyelitis admitted to the Philadelphia Hospital for Contagious Diseases from 1943 to 1945 inclusive. Patients with histories suggesting pre-existing heart disease were excluded from the study.

CLINICAL OBSERVATIONS IN 456 PATIENTS WITH NONFATAL POLIOMYELITIS

The clinical findings in 456 patients with nonfatal poliomyelitis were analyzed (Fig. 1).

Murmurs.—There were 34 (7.5 per cent) mitral and 7 (1.5 per cent) aortic systolic murmurs which were recorded upon admission of the patients to the hospital. As there have been few references made to these murmurs during subsequent examinations, their clinical course is unknown.

Arrhythmias.—Sinus tachycardia with a rate above 140 per minute, and definitely disproportionate to the body temperature, was observed in 9 cases

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(2.0 per cent). Extrasystoles were noted clinically in only 3 cases (less than 0.01 per cent).

Cardiac Enlargement.—On clinical examination, the heart was found to be enlarged in 2 patients (less than 0.01 per cent). One of these had associated electrocardiographic abnormalities; a tracing was not obtained in the other patient.

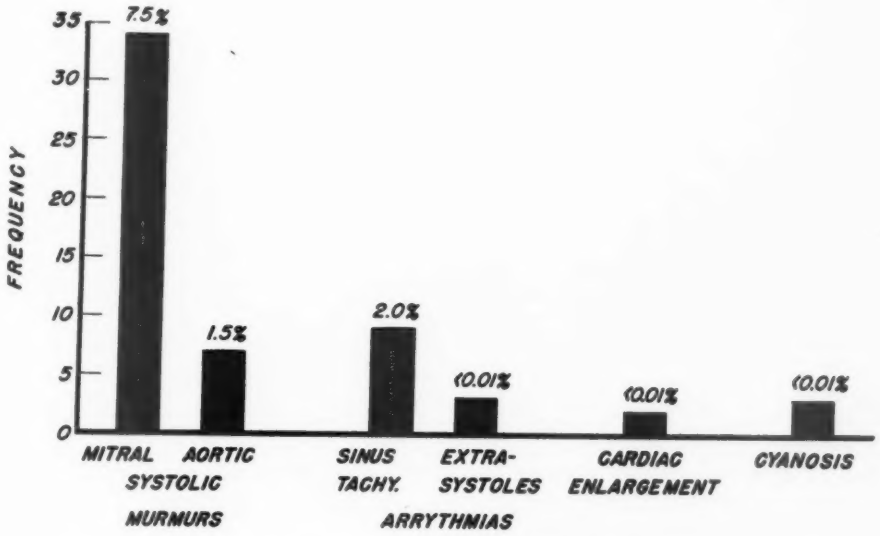

Fig. 1.—Distribution of clinical observations in 456 nonfatal cases of poliomyelitis.

Cyanosis.—Cyanosis, which required the use of the respirator, was present in 3 patients (less than 0.01 per cent). Because of their critical condition, electrocardiograms were not taken.

ELECTROCARDIOGRAPHIC OBSERVATIONS

Electrocardiograms were analyzed in 226 of the 467 patients with acute poliomyelitis (Fig. 2) and were not obtained in the remaining patients. In 32 (14.2 per cent) of the 226, the electrocardiographic pattern was abnormal.

Sex.—The electrocardiograms were abnormal in 15 (12.2 per cent) of 123 male patients and in 17 (16.5 per cent) of 103 female patients (Fig. 3). There is no significant relationship between abnormal electrocardiograms and sex.

Age.—The incidence of abnormal electrocardiograms in the various age groups (Fig. 4) was as follows: 1 to 3 years, 4 (17.4 per cent) in 23 cases; 4 to 6 years, 3 (6.7 per cent) in 45 cases; 7 to 9 years, 8 (17.4 per cent) in 46 cases; 10 to 12 years, 5 (13.1 per cent) in 38 cases; 13 to 15 years, 4 (13.8 per cent) in 29 cases; 16 to 18 years, 4 (16.7 per cent) in 24 cases; 19 to 46 years, 4 (19.0 per cent) in 21 cases. The uniform scattering of abnormal tracings in the different age groups

indicates that the age of the patient is not a significant factor in the incidence of abnormal electrocardiograms in acute poliomyelitis.

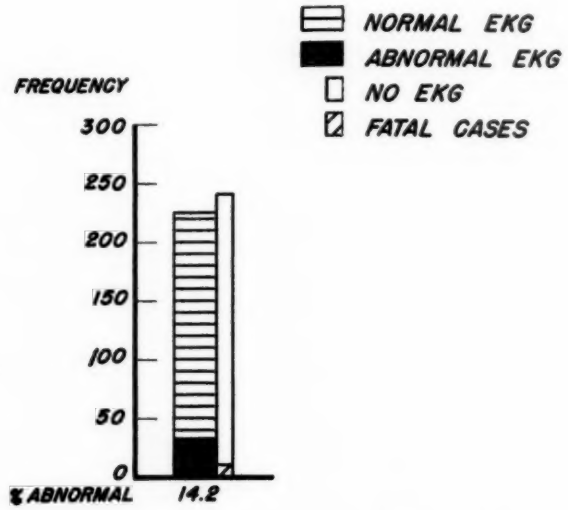

Fig. 2.—Distribution of 226 electrocardiograms in 467 cases of poliomyelitis.

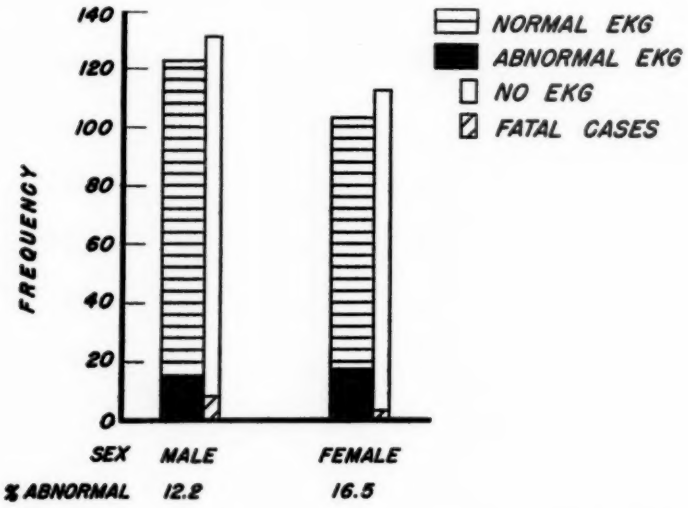

Fig. 3.—Distribution of 226 electrocardiograms in 467 cases of poliomyelitis according to sex.

Severity of Disease.—An arbitrary classification of poliomyelitis based upon the severity of the disease was devised:

Grade I—Nonparalytic type
Grade II—Involvement of one extremity
Grade III—Involvement of two or more extremities, bladder, or diaphragm
Grade IV—Bulbar or bulbospinal involvement

The cases were distributed according to this classification in order to determine the relationship between abnormal electrocardiograms and the severity of the disease (Fig. 5). The incidence of abnormal tracings was found to be

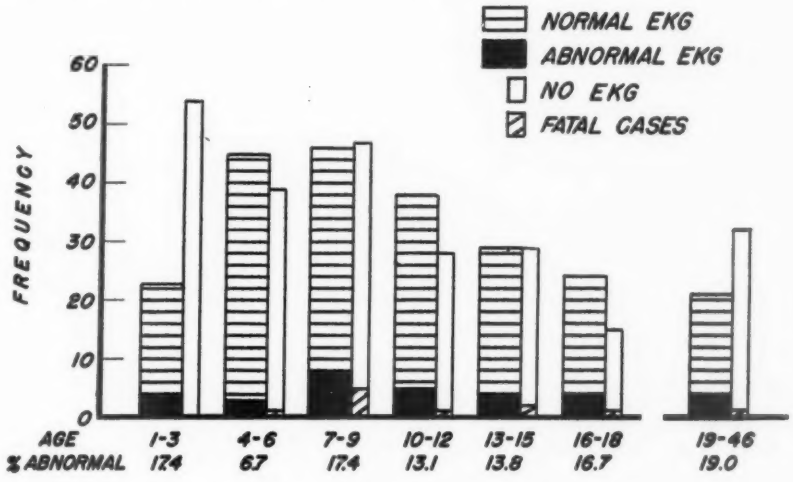

Fig. 4.—Distribution of 226 electrocardiograms in 467 cases of poliomyelitis according to age of patient.

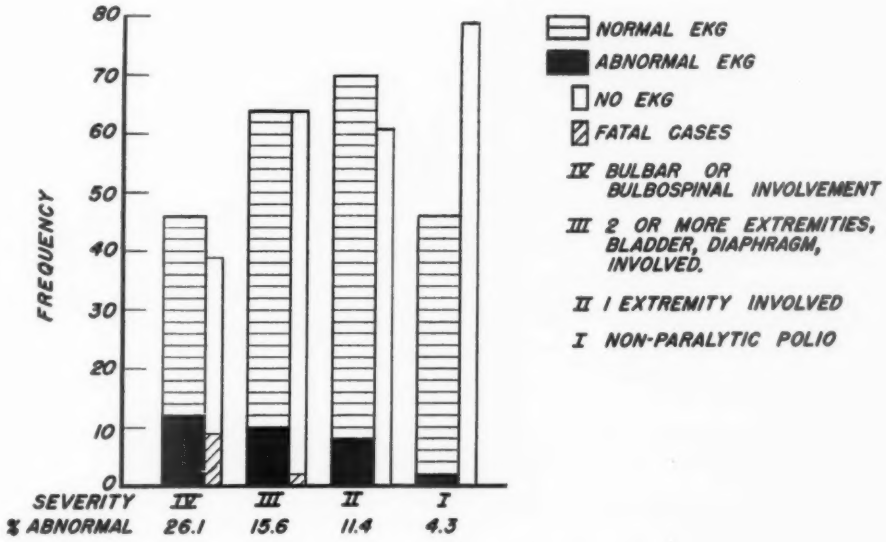

Fig. 5.—Distribution of 226 electrocardiograms in 467 cases of poliomyelitis according to severity of disease.

12 (26.1 per cent) in 46 cases of grade IV severity; 10 (15.6 per cent) in 64 cases of grade III severity; 8 (11.4 per cent) in 70 cases of grade II severity; and 2 (4.3 per cent) in 46 cases of grade I severity. The frequency of abnormal electrocardiograms rises significantly with increasing severity of the disease. This

is to be expected when one considers the uniformly high incidence of myocardial changes noted microscopically in fatal cases of poliomyelitis which are usually of grade III or grade IV severity.

Days of Fever.—Fig. 6 shows the distribution of the tracings according to the duration of the febrile period of the patients. Of 42 patients who were afebrile during their entire illness, 3 (7.1 per cent) had abnormal electrocardiograms. There were 8 patients who were febrile from one to three days; 1 (12.5 per cent) had an abnormal tracing. Forty-nine patients had fever for four to six days and 7 (14.3 per cent) showed electrocardiographic abnormalities. Of 59 patients who were afebrile after seven to nine days of illness, 7 (11.9 per cent) showed abnormal patterns. Twenty-seven patients were afebrile after ten to twelve days; 1 (3.7 per cent) of this group had an abnormal electrocardiogram. Four-

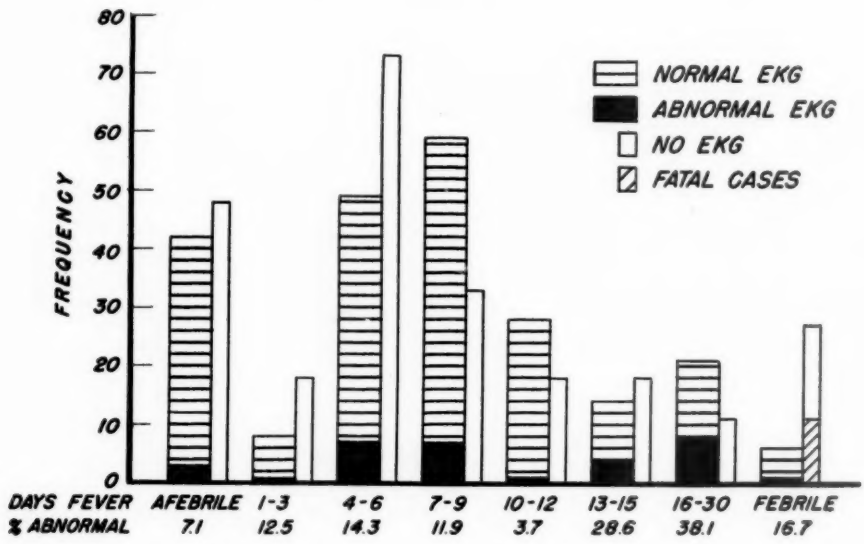

Fig. 6.—Distribution of 226 electrocardiograms in 467 cases of poliomyelitis according to days of fever.

teen patients were febrile for thirteen to fifteen days and 4 (28.6 per cent) showed abnormalities in the electrocardiogram. Twenty-one patients were febrile from sixteen to thirty days; 8 (38.1 per cent) had abnormal tracings. There were 6 patients who were febrile throughout their acute illness and 1 (16.7 per cent) had an abnormal electrocardiogram. The incidence of abnormal tracings rises inconstantly with an increase in the duration of the febrile period. Acute poliomyelitis complicated by intercurrent infection was not considered. The effect of fever per se upon the electrocardiogram was disregarded because temperature elevation influences the heart rate and does not produce the other abnormalities noted. Furthermore, in many instances the abnormalities remained after the patients became afebrile. Since there was a significant correlation between the frequency of abnormal electrocardiograms and the severity of the disease (Fig. 5),

and since the severity of the infection was associated with the duration of the febrile period, a correlation between the frequency of abnormal electrocardiographic patterns and the duration of fever could be expected. One hundred twenty patients were afebrile after seven days of illness; 13 (10.8 per cent) showed abnormal tracings. Of the 79 patients whose febrile period was longer than seven days, 19 (24.1 per cent) had abnormalities in the electrocardiogram.

Day of Initial Electrocardiogram.—The 226 tracings were arranged according to the day of the disease on which the initial electrocardiogram was taken (Fig. 7). By inspection it is evident that the abnormal tracings were scattered over a sixty-day period. The initial tracing was taken within the first two weeks of the disease in 171 cases (75.3 per cent). The lack of significant change in the frequency of electrocardiographic abnormalities as the duration of illness increased

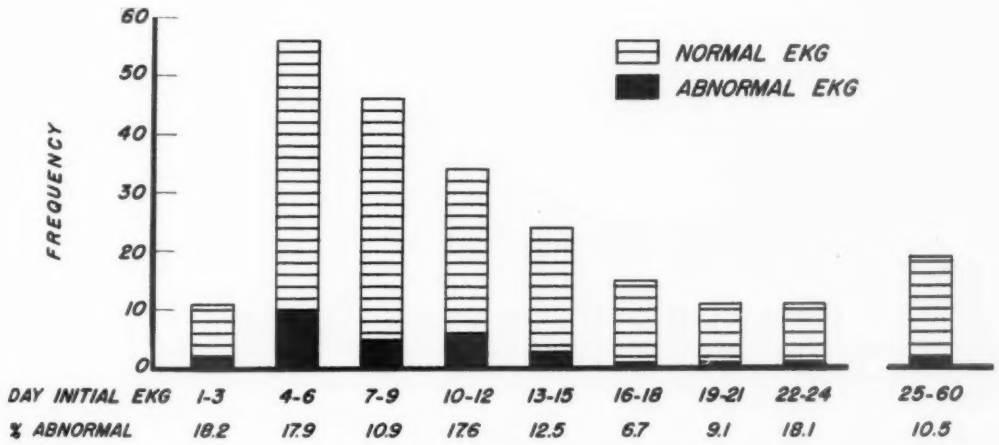

Fig. 7.—Distribution of 226 electrocardiograms in 467 cases of poliomyelitis according to day of initial electrocardiogram.

suggests that (1) the electrocardiographic abnormalities occur early in the disease, (2) they do not increase in frequency as the disease runs its course, and (3) they tend to persist for at least several weeks. The finding of continued changes in repeated tracings mitigates against the possibility of rapid return to normal. This is in agreement with Neubauer[5] who found that electrocardiographic evidence of myocarditis in diphtheria and other childhood infections (scarlet fever, pertussis, and measles) persisted for at least two to three weeks.

An analysis was made of the electrocardiographic findings in 226 patients (Fig. 8).

Arrhythmias.—Sinus tachycardia, over 140 per minute, and unquestionably disproportionate to the temperature, was observed in 9 cases (4.0 per cent). In 2 cases (0.9 per cent) extrasystoles were recorded, one of auricular and the other of ventricular origin.

P Waves.—The P waves were abnormally high and peaked in 6 cases (2.7 per cent). This was noted in Leads II and III in 4 patients and in Lead II in the 2 remaining patients.

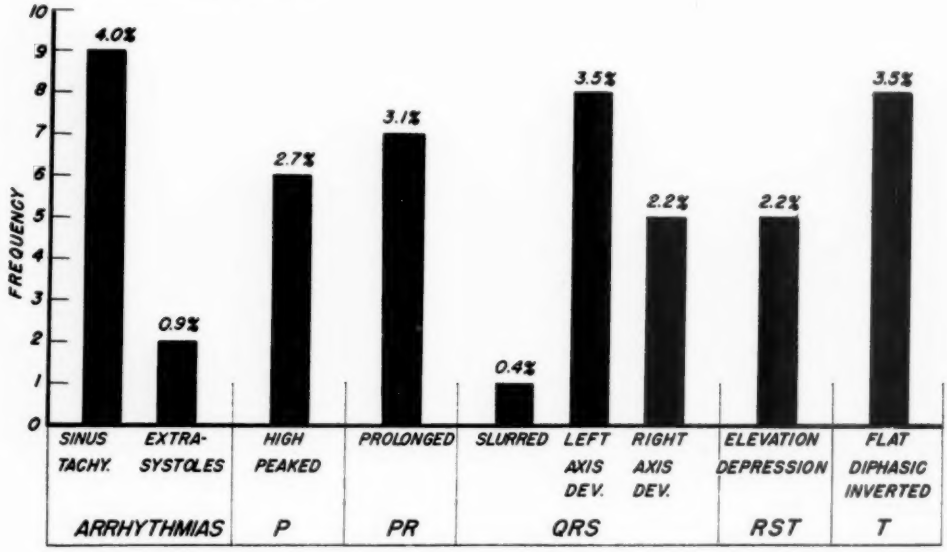

Fig. 8.—Analysis of electrocardiographic observations in 226 cases of poliomyelitis.

P-R Interval.—Abnormal prolongation of the P-R interval beyond that expected for the patient's age and heart rate (according to the scale of Ashman and Hull[6]) occurred in 7 cases (3.1 per cent). The patients ranged in age from 2 to 14 years and the longest P-R interval was 0.22 second (Fig. 9). Subsequent tracings taken from one to three weeks after the initial electrocardiogram showed improvement in 3, no change in 2, return to normal in 1, and progressive lengthening of the P-R interval in 1 case.

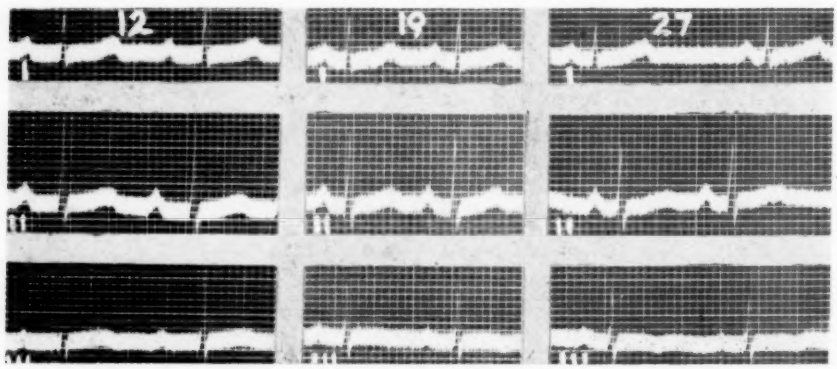

Fig. 9.—Case A-86; 9 years of age; spinal poliomyelitis (grade II severity). Twelfth day: rate, 96; P-R interval, 0.22 second. Nineteenth day: rate, 100; P-R interval, 0.16 second. Twenty-seventh day: rate, 90; P-R interval, 0.15 second.

QRS Complex.—Abnormal slurring of the QRS complex was found in Lead I in 1 case (0.4 per cent). In 8 patients (3.5 per cent) there was an unexplained left axis deviation. Although many patients presented a slight right axis deviation which was considered normal for their age, 5 (2.2 per cent), ranging in age from 10 to 16 years, showed definite right axis deviation in addition to other abnormalities (Fig. 10).

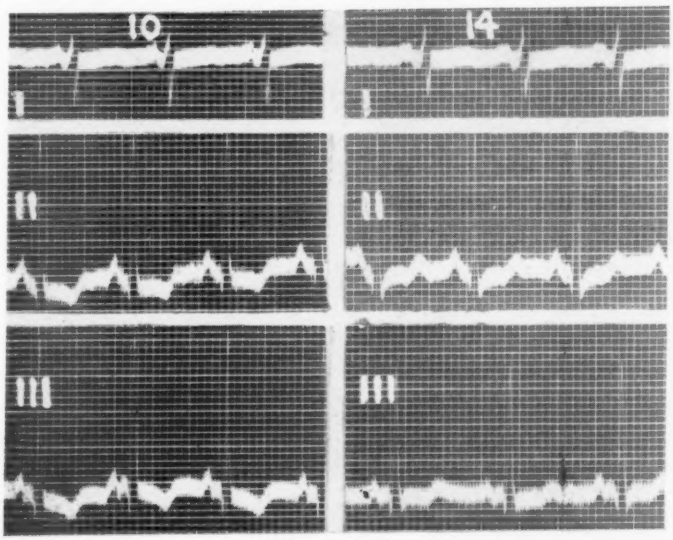

Fig. 10.—Case A-78; 10 years of age; bulbospinal poliomyelitis (grade IV severity). Tenth day: rate, 125; P-R interval, 0.14 second; depressed T_1, T_2, and T_3; S-T_2 and S-T_3 depressed; right axis deviation. Fourteenth day: rate, 120; P-R interval, 0.12 second; flattened T_1; T_2 and T_3 upright; S-T_2 and S-T_3 less depressed; right axis deviation less marked.

RS-T Segment.—Abnormal deviation of the RS-T segment from the isoelectric line was noted in 5 cases (2.2 per cent). In 1 case elevation occurred in Leads II, III, and IV F and persisted in four subsequent tracings taken over a period of two months. Another case showed RS-T elevation in Lead IV F; the abnormality was not present in a repeated tracing fifteen days later. There was depression of the RS-T segment in 3 cases. In 1 patient the change occurred in Leads I and II and was not present ten days later. In another the depression was noted in Leads II and III and persisted in a tracing taken eight days later (Fig. 10). In the third patient the depression occurred in Lead I and persisted in four subsequent tracings taken over a period of two months. This is the patient who, in addition to other abnormalities, showed RS-T elevation in Leads II, III, and IV F.

T Waves.—The T waves were flattened, diphasic, or inverted in 8 cases (3.5 per cent). This abnormality occurred in Lead I in 1 case, Leads I and II in 2 cases, Leads I, II, and III in 1 case (Fig. 10), Leads I, II, III, and IV F in 2 cases, Leads I and IV F in 1 case, and in Leads II and III in 1 case. Subsequent tracings were obtained in 7 of the 8 cases, with improvement or exaggeration of the abnormality in 5 and no change in 2 cases.

EVALUATION OF ELEVEN FATAL CASES

Eleven (2.4 per cent) of the 467 patients with acute poliomyelitis succumbed. Unfortunately, tracings were not obtained in these patients because of their grave condition. A clinical analysis of the fatal cases (Table I) reveals that 9 of the 11 patients had poliomyelitis of Grade 4 severity and 2 of Grade 3; all were febrile from the onset of their illness until death; cardiac enlargement was noted in 2 cases, mitral systolic murmurs in 2 cases, and heart rates over 140 per minute in 2 cases; cyanosis was recorded in 10 of the 11 patients. Age, sex, and race were not important factors in this group.

Autopsies were performed on 6 of the 11 patients. The cardiac findings (Table II) consisted of subepicardial petechiae in all 6 cases, dilatation of the right ventricle in 2, dilatation of both ventricles in 1, decreased consistency of the myocardium in 4, and no gross abnormalities in 1 case. Microscopic examination of the heart in 4 cases showed interstitial edema in all 4, congestion in 3, and perivascular and interstitial cellular reaction in 2 cases. Accompanying changes in the lungs in 6 cases (Table III) included congestion in all 6, edema in 4, subpleural hemorrhages in 2, interstitial pneumonitis in 3, patchy atelectasis in 2, terminal aspiration pneumonia in 2, and lymphoid hyperplasia of the bronchial walls in 3 cases.

TABLE I. CLINICAL SUMMARY OF ELEVEN DEATHS FROM POLIOMYELITIS

CASE	AGE	SEX	COLOR	SEVERITY	DAYS OF FEVER	CLINICAL FINDINGS IN HEART			
						MURMURS	TACHYCARDIA	CARDIAC ENLARGEMENT	CYANOSIS
1	7	M	W	IV	Febrile	o	+	o	+
2	10	M	W	IV	Febrile	o	o	o	+
3	8	M	W	IV	Febrile	o	o	o	+
4	9	M	W	IV	Febrile	+	+	o	+
5	9	F	W	IV	Febrile	o	o	o	+
6	14	M	W	IV	Febrile	o	o	o	+
7	8	M	W	III	Febrile	+	o	+	+
8	14	F	W	IV	Febrile	o	o	o	+
9	17	M	W	IV	Febrile	o	o	+	+
10	6	F	W	IV	Febrile	o	o	o	+
11	41	M	W	III	Febrile	o	o	o	Not recorded
Totals						2	2	2	10

TABLE II. PATHOLOGIC FINDINGS IN THE HEART IN FATAL CASES OF POLIOMYELITIS (SIX AUTOPSIES)

CASE	GROSS			MICROSCOPIC		
	SUBEPICARDIAL PETECHIAE	VENTRICULAR DILATATION	DECREASED CONSISTENCY MYOCARDIUM	INTERSTITIAL EDEMA	CONGESTION	PERIVASCULAR AND INTERSTITIAL CELLULAR INFILTRATION
1	+	0	+	+	+	0
2	+	Right	+	+	+	+
3		No autopsy				
4	0	0	+	+	+	+
5	+	Right	0	+	0	0
6		No autopsy				
7		No autopsy				
8		No autopsy				
9	+	Right and left	+	No microscopic study		
10	0	0	0	No microscopic study		
11		No autopsy				
Total	4	3	4	4	3	2

TABLE III. PATHOLOGIC FINDINGS IN LUNG IN FATAL CASES OF POLIOMYELITIS (SIX AUTOPSIES)

FINDING IN LUNG	NUMBER OF CASES
Congestion	6
Edema	4
Subpleural hemorrhages	2
Interstitial pneumonitis	3
Patchy atelectasis	2
Aspiration pneumonia	2
Lymphoid hyperplasia of bronchial walls	2

DISCUSSION

The cardiac abnormalities detected clinically in the present study of acute poliomyelitis were insufficient to warrant a diagnosis of myocarditis. According to Neubauer,[5] however, myocarditis may exist in certain acute infectious diseases even though clinical findings are slight or absent. The mitral and aortic systolic murmurs found are difficult to evaluate inasmuch as they often occurred in

febrile patients and in conjunction with normal tracings. The murmurs in poliomyelitis certainly do not indicate valvular disease, unless the latter preexisted. Sinus tachycardia, unless persistent, and premature contractions without additional evidence of cardiac involvement do not constitute heart disease, but the presence of either disturbance merits a complete cardiac evaluation. It is obvious that cardiac enlargement or unexplained cyanosis likewise should be investigated fully. One hesitates to interpret the high, peaked P waves as indicative of auricular disease, especially in the absence of notching or widening. The fact that the P-wave abnormalities disappeared in repeated tracings in some patients suggests that their presence might have been due to a toxic effect of the disease. The abnormally prolonged P-R intervals, which changed considerably in most instances, may represent true A-V conduction defects. The slurred QRS complex in Lead I in one patient probably signifies a myocardial abnormality, as the complex was of average amplitude. The finding of left axis deviation in children may possibly be abnormal, although the cause for this condition was obscure. Right axis deviation occurred frequently in young patients but was noted only if there were associated abnormalities. In some of these patients the axis deviation was marked. Significant deviation of the RS-T segment is reasonable evidence of a myocardial disorder. Inversion or flattening of the T wave in Lead I may be interpreted in the same light.

The question of the influence of electrolyte imbalance upon the electrocardiogram arises when one considers that the disease was prevalent in the summer months and the patients were generally treated with hot packs. This possibility is excluded on the basis that the fluid balance of the patients was maintained and sufficient salt supplied. The effects of electrolytic disturbances upon the Q-T interval were not observed in any of the tracings.

The only drugs received by some of the patients which conceivably might have influenced the electrocardiographic pattern were prostigmine and atropine. These drugs were given to all patients with acute poliomyelitis in 1943, to alternate patients in 1944, and to none of the patients in 1945. Prostigmine was used in doses of 10 to 15 mg. and atropine in doses of 0.2 to 0.3 mg. orally three times a day for two weeks. A few patients received 0.5 to 1.0 mg. prostigmine and 0.2 to 0.3 mg. atropine intramuscularly for one week. In only one of the thirty-two patients with abnormal tracings was there a possible time relationship between the use of the drugs and the electrocardiographic abnormalities. The RS-T segment was depressed in Leads I and II in this patient. No other abnormalities could be attributed to the use of medication. Digitalis had not been administered to any of the patients who showed electrocardiographic changes.

If the pathologic findings in the present study may be correlated with the electrocardiographic abnormalities, it is reasonable that a poliomyelitic myocarditis may be suspected by electrocardiogram. As certain of the microscopic changes observed represent toxic, degenerative, or anoxic effects, with or without inflammatory reaction, one may infer only that myocardial derangement exists, particularly since the changes in the electrocardiograms are neither uniform nor specific.

The fatal cases presented little clinical evidence of cardiac disease. The cyanosis of these patients was more likely due to respiratory paralysis than to myocardial involvement. Tracings in these cases might have contributed to a better understanding of myocardial disease in poliomyelitis.

In this study the electrocardiograms were more instructive than were the clinical findings in determining the presence of myocardial derangement. The correlation of electrocardiographic abnormalities with severity of infection and the finding of myocardial changes in a high percentage of fatal cases make a thorough study of the cardiovascular system a necessity in all patients with severe poliomyelitis. Since abnormalities occur early in the disease, tracings should be taken as soon as possible. Serial electrocardiograms showing the progress of the changes are more informative than isolated tracings.

SUMMARY

1. The cardiac status of 467 patients suffering from acute anterior poliomyelitis is reviewed.

2. Electrocardiographic abnormalities appeared in 32 (14.2 per cent) of 226 patients. A significant correlation exists between the frequency of abnormalities and the severity of the disease. Electrocardiographic changes may occur early in this disease and tend to persist for at least several weeks.

3. In all patients in whom abnormalities are detected, serial electrocardiograms are recommended.

4. Autopsies performed in six of eleven fatal cases revealed pathologic changes in the myocardium in all but one instance.

We are indebted to Dr. A. C. LaBoccetta, Chief Resident Physician, Philadelphia Hospital for Contagious Diseases, for valuable suggestions in the preparation of this study.

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Clinical Reports

LUTEMBACHER'S SYNDROME COMPLICATED BY ACUTE BACTERIAL ENDOCARDITIS

Report of a Case Diagnosed During Life

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THE association of a large interauricular septal defect and mitral stenosis (Lutembacher's syndrome) is relatively rare, and the complication of this combination of lesions by bacterial endocarditis has been clearly described in but one previous case[2]; a second instance was briefly alluded to by Jacobius and Moore.[3] The case herein described therefore seemed worthy of record.

In all probability the occurrence of the Lutembacher syndrome is much less rare than its infrequent clinical recognition would imply, yet the diagnosis can probably be made with reasonable certainty in most cases as the features of the syndrome become more widely known.

CASE REPORT

C. B., a 44-year-old white Canadian spinster and clerical worker in the New Haven Hospital, was first seen in the outpatient clinic in 1934 where she presented herself for a routine employee's examination. She offered no complaints but remarked that she had been known to have had high blood pressure for at least two years, that both parents and two siblings had died of high blood pressure and apoplexy, and that six living siblings also had high blood pressure (all six died within the next decade of either cerebral vascular accidents or congestive heart failure).

The patient had had influenza in 192), a tonsillectomy in 1923, and no other known illness. She specifically denied rheumatic fever and chorea by name and symptoms, and she did not recall having had many sore throats as the indication for the tonsillectomy. On systemic review of symptoms she acknowledged occasional awareness of irregularity in the beating of the heart, that her ankles were sometimes slightly swollen toward the end of the day, and that exertion evoked dyspnea but that ordinary activities did not cause breathlessness; she denied orthopnea and paroxysmal dyspnea. She had never been cyanotic so far as she was aware.

Examination on this occasion disclosed a well-developed and well-nourished woman with normal coloration. The blood pressure was 220/130 in both arms and slightly higher in the legs. The retinal vessels revealed only minimal sclerotic changes. The heart seemed slightly enlarged, there was an apical systolic shock, and a loud sytolic murmur was audible over the entire pre-

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cordium. No signs of congestive failure were detected. Renal function studies gave normal results, and the Kahn test for syphilis was negative. A diagnosis of hypertensive cardiovascular disease was made, and for a few months the patient received at first small and later large doses of potassium thiocyanate (serum concentrations reached 10 to 20 mg. per cent) without convincing influence on the fluctuating blood pressure, which declined as low as 160/105 during control periods as well as during thiocyanate medication. The patient lost interest in the therapeutic efforts and terminated her visits.

Five years later she returned for a few months for the symptomatic treatment of occasional generalized headache associated with vomiting. At this time a systolic thrill over the precordium was noted together with a harsh systolic murmur transmitted to the left infrascapular region, and the apical first sound was described as increased in intensity and rumbling in quality. The electrocardiogram (Fig. 1) showed prolonged A-V conduction, right axis shift, abnormally tall,

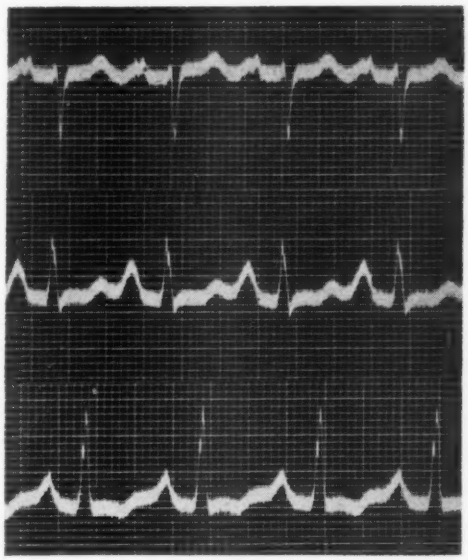

Fig. 1.—Electrocardiogram made in 1939. The tracing shows long P-R intervals, slurred QRS complexis, tall notched P waves, and right axis deviation.

broad, and notched P waves, and slurring of QRS complexes. The question of a congenital anomaly was raised for the first time. Roentgenographic study of the heart (Fig. 2) disclosed marked enlargement of the left ventricle as well as marked prominence of the pulmonary conus and arteries, and a diagnosis of a patent ductus arteriosus and interventricular septal defect was ventured. Contact with the patient was again lost for three years.

In January, 1943, the patient was admitted to the New Haven Hospital for an acute respiratory illness which proved to be lobar pneumonia of the right upper and middle lobes, and pneumococcus type III was recovered from the sputum and the blood. On this occasion there was moderate cyanosis of the lips and nail beds, and ectopic ventricular beats were detected. She was treated with digitalis and sulfamerazine, the temperature fell to normal within three days, the cyanosis promptly disappeared, and a complete recovery was made. The blood pressure ranged from 200/114 to 130/80 during hospitalization. The arm-to-tongue circulation time (with decholin sodium) was twenty seconds and the venous pressure (direct method) was 6.5 cm. of water; these observations were made after digitalization.

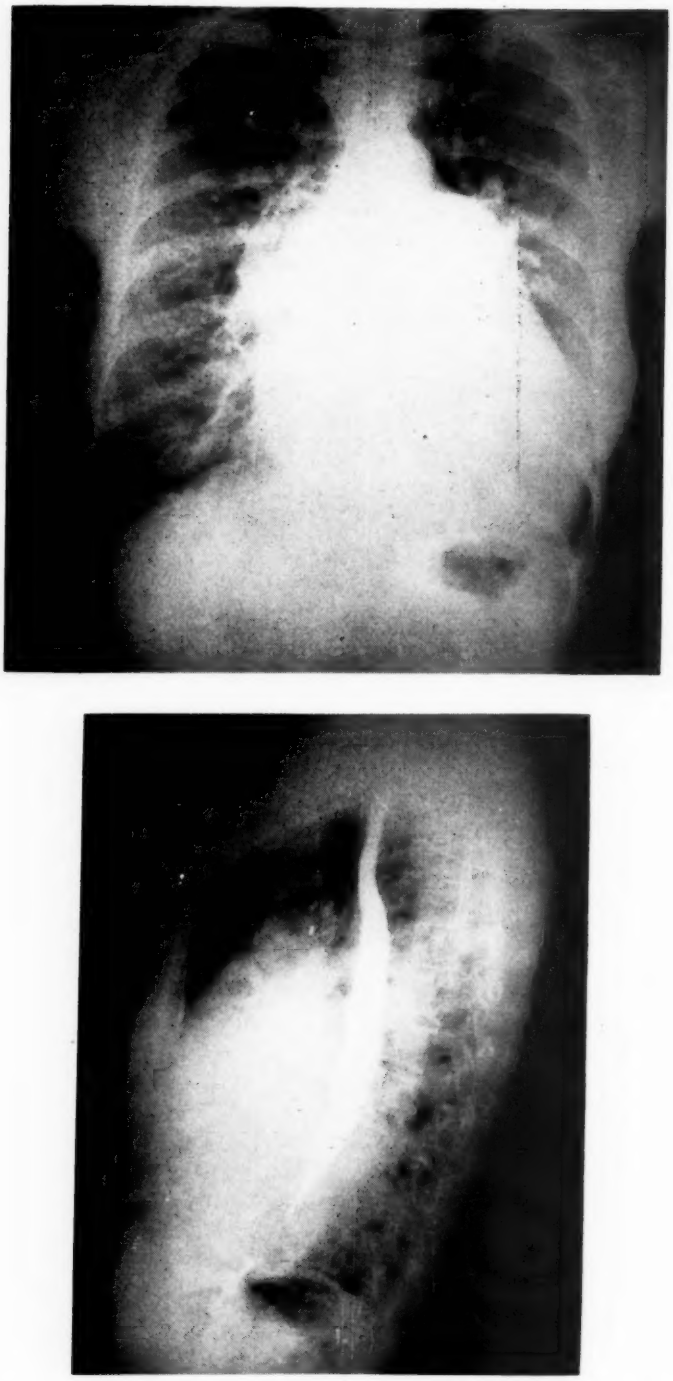

Fig. 2.—X-ray films made in 1939. There is enlargement of the left ventricle and prominence of the pulmonary conus and arteries.

The patient was discharged on the eleventh day following admission. She discontinued the digitalis a month later and maintained her usual satisfactory state of health until December, 1944, when fatigue became a conspicuous symptom. She consulted a physician who discovered râles at the right apex and demonstrated pulmonary infiltration on the right side by roentgenographic examination (Fig. 3). She was advised to stop work and was placed at bed rest. She did not improve, and in February, 1945, she developed severe pain low in the back; lesser pains involved the right knee and shoulder, but the joints were not swollen, hot, or reddened. Presently anorexia and night sweats appeared, but she was unaware of fever. On a few occasions red spots were noted on the trunk, but the patient recalled no soreness of the fingers. She re-entered the hospital on March 8, 1945. Her age at this time was 55 years.

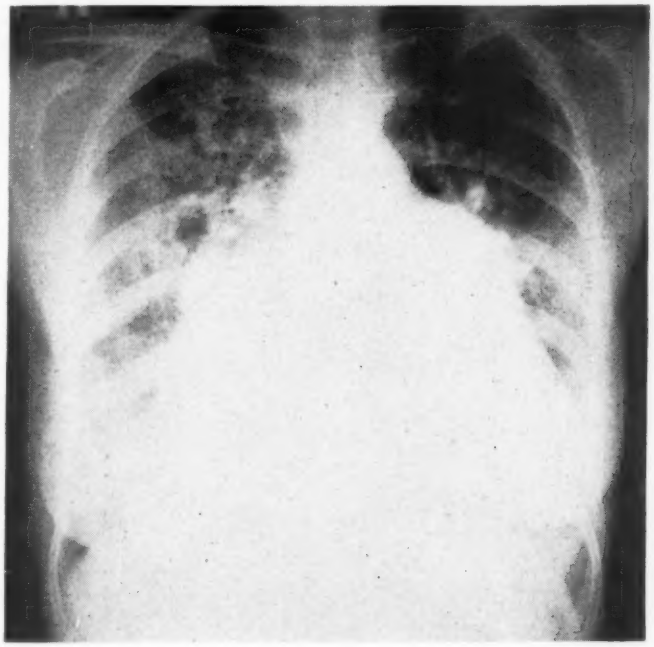

Fig. 3.—X-ray film made in January, 1943. In addition to the findings noted in 1939, there is now pulmonary infiltration on the right side.

On admission for this last hospitalization, the patient was acutely ill, weak, and perspiring but not cyanotic. Her speech was slow and thick. Rectal temperature was 101.5° F. The blood pressure ranged between 120/84 and 116/78. The upper half of the right lung field and the lower half of the left revealed dullness and moist râles in abundance. The cardiac signs recorded were as follows: evidence of a huge heart (a diffuse apex impulse was apparent in the fifth and sixth left intercostal spaces in the region of the apex, and the impulse was visible in the midaxillary and posterior axillary lines), a fundamentally regular rhythm with frequent ectopic ventricular beats, a loud and harsh systolic murmur audible all over the precordium, and a low-pitched rumble in the latter half of diastole with presystolic accentuation in the region of the apex; the apical first sound was loud and sharp, and the pulmonic second sound was abnormal in that it exceeded the aortic second sound in intensity. A presystolic precordial thrill was described by several observers. The liver was moderately enlarged, there were signs suggestive of ascites, and marked tenderness was present in both costovertebral angles. There was no peripheral edema, and the fingers were not clubbed. Two red spots suggesting petechiae were noted on the lower

eyelids, and one small hemorrhage was seen in the right retina. The red blood cell count was 5.56 millions per cubic millimeter and the hemoglobin was 14 grams. The white cells numbered 25,600 per cubic millimeter, of which 68 per cent were polymorphonuclear cells. The corrected erythrocyte sedimentation rate was 22 mm. per hour (Wintrobe method). The urine specific gravity was 1.023, albumin was Grade 2, and the centrifuged sediment contained a moderate number of white cells as well as hyaline and granular casts. The blood nonprotein nitrogen was 95 mg. per cent. Venous pressure was 14.5 cm. of water, and the circulation time from arm to tongue was 23 seconds. The electrocardiogram (Fig. 4) disclosed sinus rhythm with prolonged A-V conduction time, abnormally broad and notched P waves, frequent ectopic ventricular beats, right axis shift, abnormal slurring of the QRS complexes in the limb leads, and T waves that were abnormal in being flat in Lead I.

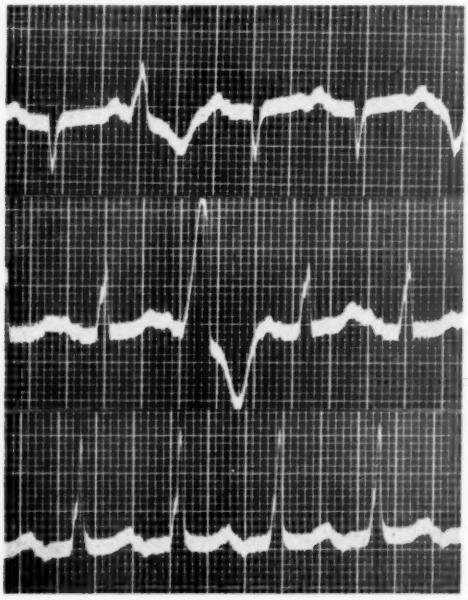

Fig. 4.—Electrocardiogram made in March, 1945. The principle findings are long P-R intervals, frequent ectopic ventricular beats, right axis shift, slurring of the QRS complexes, and flat T waves in Lead I.

The course in the hospital was brief and dramatic. Because of evidence of heart failure, the patient was rapidly digitalized with 4 units of digifolin given parenterally. The persistence of blood pressure at an unusually low level for the patient and the development of oliguria led to the transfusion of 500 c.c. of blood and the slow intravenous injection of 1,500 c.c. of 5 per cent glucose solution, but no apparent benefit ensued. A culture of the blood, taken on admission, revealed pneumococcus type V at the end of forty-eight hours, confirming a prior suspicion of bacterial endocarditis. Treatment with penicillin was promptly instituted; 50,000 units were given intravenously at once, and a slow intravenous infusion of 300,000 units per day was continued. However, that evening there appeared a livid discoloration of the face which by the next morning had become purple and had spread to the neck and shoulders (Fig. 5). The blood pressure continued to decline slowly in spite of another transfusion of blood, the extremities became cold and mottled, respirations grew gradually more labored, coma ensued, and the patient died in the afternoon of the fourth hospital day.

The final clinical diagnosis was acute bacterial endocarditis complicating a congenital cardiac anomaly consisting of a large interauricular septal defect with associated mitral stenosis (Lutembacher syndrome). The pulmonary lesions were suspected to be infarcts, and the renal pathology was attributed to the bacterial endocarditis with either embolic or toxic injury.

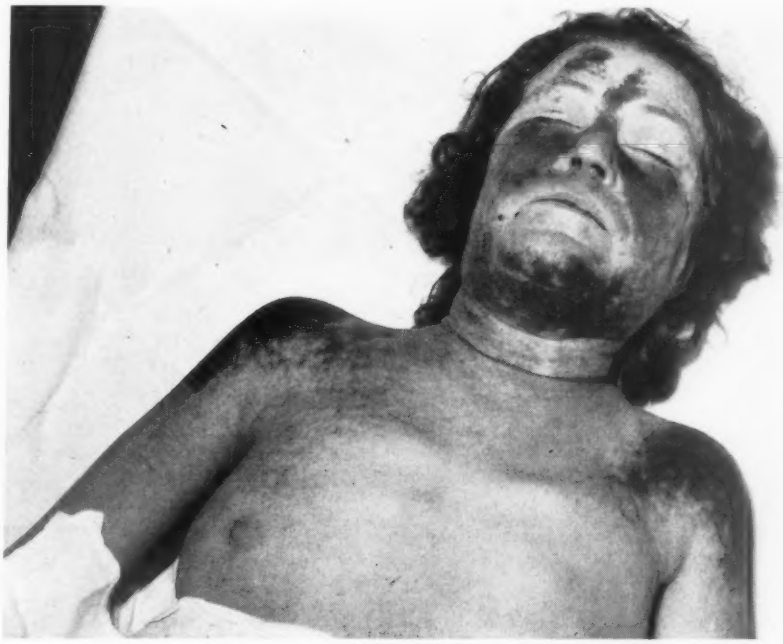

Fig. 5.—Showing the hemorrhage into the skin of the face and shoulders.

Diagnostic Discussion.—Each of the authors independently interpreted the cardiac abnormality before death as Lutembacher's syndrome. The diagnosis was made with complete conviction on the basis of the following arguments:

1. The loud, harsh, widely radiating precordial *systolic* murmur and thrill, first noted in 1940, was considered referable to the markedly increased blood flow through the greatly enlarged pulmonary artery which was known to be present from previous roentgen examinations. Only a few lesions could yield these signs: an arteriovenous fistula between the aorta and pulmonary artery, an aneurysm of the pulmonary artery, or a large auricular septal defect with considerable shunting of blood from the left auricle to the right. The last seemed the most acceptable in view of the electrocardiographic features discussed below. The additional presence of mitral stenosis seemed established by the classical physical signs of that lesion: shocklike apical first sound, low-pitched apical diastolic murmur with presystolic accentuation, and apical diastolic thrill noted in the last illness.

2. The electrocardiographic features of marked right axis shift (in spite of considerable hypertension in the past), and the tall, broad, and notched P waves (implying auricular hypertrophy; right, rather than left, for the lateral roentgeno-

gram showed no enlargement of the left auricle) seemed entirely logical developments of a large left-to-right auricular shunt, causing overloading of the right auricular and right ventricular chambers with sufficient hypertrophy of the latter to overbalance the effects of the chronic hypertension on the electrocardiographic axis. The long P-R interval could be attributed either entirely or in part to abnormally long conduction time within the enlarged right auricle or to a large interauricular septal defect located sufficiently low to affect the A-V node.

3. The extraordinarily prominent pulmonary artery and branches in the roentgenogram of the chest was considered typical of interauricular septal defect with a large shunt. Pulmonary artery enlargement of this unusual degree is not, in our experience, seen with patent ductus arteriosus (the previous roentgen diagnosis) and was regarded as a highly unlikely expression of mitral stenosis alone, particularly in view of the absence of enlargement of the left auricle. A large aortic-pulmonary artery fistula seemed excluded by the absence of a wide pulse pressure and by the long course without heart failure; moreover, neither this lesion nor aneurysm of the pulmonary artery could account for the abnormal auricular electrocardiogram.

4. Although primary chronic rheumatic myocarditis and high-grade mitral stenosis and insufficiency could also explain the electrocardiographic abnormalities, roentgenographic study failed to show the expected enlargement of the left auricle. Moreover, mitral stenosis of such extreme degree as to result in the enormous cardiac enlargement would probably have led to congestive failure long before the terminal illness. That "incidental" mitral stenosis could, nevertheless, be present without left auricular enlargement seemed acceptable on the basis of an auricular septal defect sufficiently large to receive a considerable part of the left auricular blood, thereby avoiding strain of the left auricle.

The diagnosis of the Lutembacher syndrome was thus made clinically.

*Necropsy Findings**.—The heart weighed 695 grams. In situ, it was seen that almost the entire anterior surface of the heart was composed of right auricle and right ventricle. The pulmonary conus was extremely large. On opening the right auricle a large circular defect measuring 3.0 cm. in diameter involved the anterior superior part of the septum (Fig. 6). The valve measurements were as follows: tricuspid, 14 cm.; pulmonic, 9.5 cm.; mitral, 7 cm.; and aortic, 6.5 cm. The right ventricle was 8 mm. thick and the left ventricle 12 mm. thick. The right auricle and ventricle were tremendously dilated. The mitral valve showed thickening and rolling of the free edges with marked thickening and fusion of the chorda tendineae. Engrafted on the right leaflet of the mitral valve was a large, red, friable, and fungating thrombus which extended outward and partially blocked the mitral orifice (Figs. 6 and 7). The free edge of the tricuspid valve was edematous. The cusps of the aortic valve showed a very slight degree of fusion at the commissures. The pulmonary valve was not remarkable. A microscopic section of the mitral valve revealed an acute process with necrotic polymorphonuclear leucocytes and a vegetation made up of clumped fibrin, acute inflammatory cells, and clumps of gram-positive cocci.

There were numerous small, red, wedge-shaped infarcts in the right lung. Both lungs showed small areas of focal pneumonia. There was a septic infarct in the spleen. A section of skin from the area of livid cyanosis revealed a great deal of hemorrhage below the epithelium, and there was a marked acute arteritis with necrosis of some of the artery walls, while other arteries were plugged with small hyaline thrombi. The other organs were not remarkable.

*The autopsy was performed by Dr. Herbert Axilrod, Department of Pathology, Yale University School of Medicine.

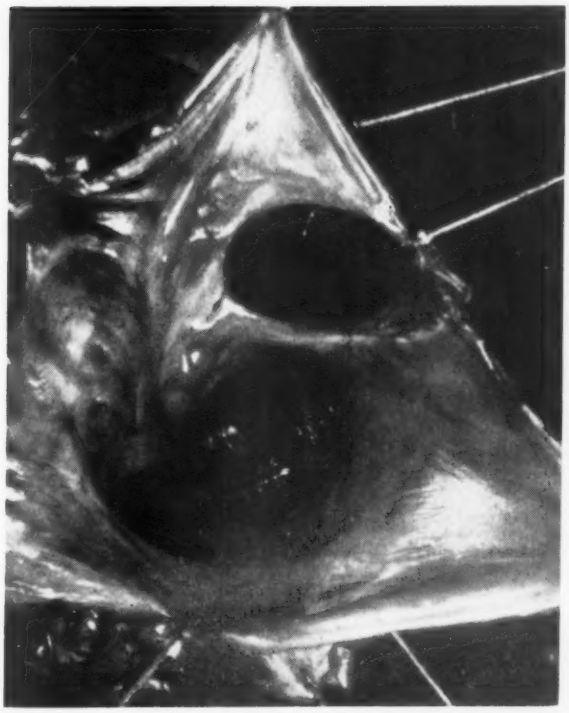

Fig. 6.—Showing the opened left auricle disclosing the large defect in the auricular septum and the vegetation on the mitral valve.

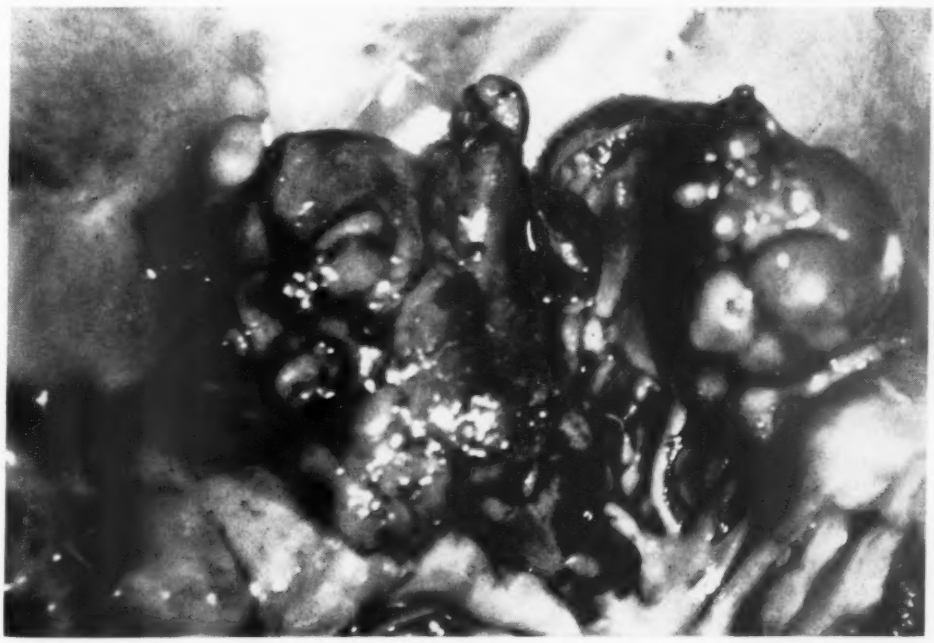

Fig. 7.—Showing a close-up view of the massive vegetation on the mitral valve.

COMMENTS

It was noted that the patient was not ordinarily cyanotic, which is consistent with the arteriovenous direction of the blood flow that prevails with interauricular septal defects. The cyanosis that appeared late in the terminal illness implies that a reversal of the shunt to a veno-arterial direction had developed, and this would be a logical result of ultimate dilatation and failure of the chronically overstrained right ventricle. Moreover, lesions of the lung, such as infarcts seen at necropsy, could have contributed to the cyanosis. The intense and livid cyanosis that spread over the face, neck, and upper thorax during the last twelve hours of life seems to have been due to bleeding from arterioles in the skin; similar livid cyanosis has been mentioned as a terminal event in other cases of Lutembacher's syndrome without comment as to vascular lesions in the skin or association with bacterial endocarditis.[1]

It is regrettable, in retrospect, that the early suspicion of bacterial endocarditis did not lead to the prompt institution of penicillin therapy, for when the diagnosis was proved by blood culture, the loss of forty-eight hours' time in the presence of an acute pneumococcal infection probably accounted for the therapeutic failure. Success in the treatment of *acute* bacterial endocarditis demands institution of penicillin therapy at the earliest suspicion of the diagnosis without waiting for the results of blood cultures.

When the diagnosis of acute bacterial endocarditis became established, the pulmonary lesions were attributed to embolism in the pulmonary circulation; the urinary abnormalities and the conjunctival and retinal hemorrhages were viewed as due to emboli in the systemic circulation. The presence of vegetations in close relation to the septal defect or on the adjacent aortic cusp of the mitral valve is ideal for the discharge of emboli into both circulations for, on the one hand, significant volume of blood flows from the higher-placed left auricle into the right side of the heart and pulmonary arteries and, on the other hand, emboli from mitral vegetations would readily enter the left ventricle and systemic arteries. Since at necropsy there were no vegetations near the septal defect, it is presumed that emboli reached the left auricle from mitral regurgitation and that from the left auricle they were swept into the right auricle and the pulmonary circulation.

Survival into the sixth decade is unusual for patients with Lutembacher's syndrome; only four of the twenty-four patients reported on by McGinn and White[1] lived beyond the age of 50 years. Had bacterial endocarditis not supervened, the patient might well have lived considerably longer, for no significant degree of heart failure had developed prior to the terminal illness.

The anatomic characteristics of a rheumatic etiology for the mitral stenosis support those who contend that the mitral lesion is an acquired rather than a congenital accompaniment of the auricular septal defect in Lutembacher's syndrome.

SUMMARY

A case of auricular septal defect with associated mitral stenosis (Lutembacher's syndrome) complicated by bacterial endocarditis is described.

The diagnosis of Lutembacher's syndrome was made clinically and confirmed at necropsy. The diagnostic features are discussed.

The mitral stenosis proved to be of rheumatic etiology.

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THE TETRALOGY OF FALLOT

An Account of a Patient With This Condition Surviving Over Forty-Five Years

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THE remarkable combination of congenital cardiac anomalies termed the tetralogy of Fallot presupposes serious circulatory handicaps from early fetal existence. Hence, Abbott's figure[1] of an average life span of 12 years and 9 months for such subjects is not surprising. The survival of subjects with the tetralogy of Fallot to midlife is worthy of note. White and Sprague[2] record an isolated instance of survival to the sixtieth year. Strandell's patient[3] lived fifty-six years and three months, and that of Volini and Flaxman[4] lived forty-one years. The last two cited subjects died of causes other than their congenital cardiac lesions. The patient herein considered pursued a useful career as an electrical engineer and succumbed to congestive failure at the age of 45 years and 4 months.

Although the patient had been a blue baby, the congenital lesion was not recognized until the third year of life. In the interval between his matriculation at the University of Wisconsin in 1919 and his death in 1945, repeated observations were made. The physical limitations imposed on him by dyspnea, cardiac consciousness, and fatigability were met by an indomitable will and such adjustments as reconciled the task at hand to his cardiac reserve. A responsible postion was attained in his professional field. Because of recurrent episodes of tonsillitis, tonsillectomy was performed in 1922. Cholecystectomy became imperative in 1925. Both surgical procedures were well withstood. In 1935 a cerebral vascular accident was manifested by dysarthria, left hemiplegia, and hemiparesthesia. Within ten days, only minor residua of the neurological lesion (slight ptosis of the left upper lid, flattening of the left nasolabial fold, and questionable weakness of the grip in the left hand) could be demonstrated.

The terminal decline was initiated by an upper respiratory infection in November, 1944. Dependent edema advanced from the feet to the legs and to the thighs and the flanks in turn. After a short remission under therapy and rest in the hospital, dyspnea and edema advanced apace. His physical status on the last admittance to the State of Wisconsin General Hospital may be summarized thus: Pronounced cyanosis of the lips, ears, and fingers, obvious dyspnea, gross clubbing of the fingers and toes, extreme engorgement of the veins of the neck, marked edema of the left arm, legs, and trunk up to the flanks, systolic thrill over the left subclavian artery, fine crackling and medium moist râles at both bases, and a palpable liver 3 cm. below the costal margin. The cardiac findings included a diffuse wavy impulse over the entire precordium with accentuation in both second intercostal spaces, systolic thrill in the right second intercostal space, and double thrill in the left second intercostal space. The cardiac borders were percussed as shown in Table I.

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TABLE I

RIGHT (MM.)	INTERCOSTAL SPACE	LEFT (MM.)
45	II	60
60	III	140
72	IV	150
	V	Axilla
	VI	Axilla

Systolic murmurs were heard over the entire precordium. The basal systolic murmur was coarser in quality and was transmitted from the point of maximum intensity in the second left intercostal space to the neck. A diastolic element of this murmur was audible in the second and third left intercostal spaces. A second systolic murmur was heard best in the fourth and fifth left intercostal spaces close to the sternum and was transmitted for considerable distances toward both axillae.

Over a period of fifteen years, evidence of progressive myocardial change had been manifested in electrocardiograms. Initial prolongation of the auriculoventricular conduction (0.24 second) had advanced to 0.32 second without comparable intraventricular delay (0.08 to 0.09 second). The earliest available blood count (May 6, 1920) revealed a polycythemia (hemoglobin, 128 per cent; erythrocytes, 7,010,000 per cubic millimeter). Although fluctuations occurred, the erythrocytosis persisted throughout life (Nov. 23, 1945, hemoglobin, 19.6 Gm. per 100 c.c., or 117 per cent; erythrocytes, 5,160,000; hematocrit readings, 62 and 61 per cent).

The usual supportive measures were supplemented by venesection and the administration of oxygen during the period of the terminal illness. The compensatory order of the polycythemia was appreciated, but it was hoped that temporary improvement through a lessening of the total cardiac load and a decrease in the viscosity of the blood might be accomplished by venesection. The attempt was technically inadequate, so that no conclusion could be derived. Oxygen gave remarkable subjective and objective relief. Sleep was afforded by this means when sedatives alone had become ineffective.

In spite of all therapeutic efforts, the patient's condition after the last admission became steadily worse, and he died Dec. 6, 1945.

Autopsy Findings.—The external appearance has been described in the clinical notes. The heart weighed 790 grams. The aortic and pulmonic orifices were preserved unopened. The mitral orifice measured 12 cm. in circumference; the tricuspid, 15 centimeters. The right ventricular wall was from 0.3 to 1 cm. thick; the left, from 0.9 to 1.1. centimeters. The epicardium was smooth and glistening, but on the serous surface of the right auricular appendage there were several pale irregular, flat, raised areas up to 3 mm. in diameter. The myocardium was gray-pink and firm, and slight scarring was visible grossly.

A defect 3 cm. in diameter was found in the extreme upper part of the interventricular septum. The margins of this defect were smooth and rounded (Fig. 1). The aortic valvular orifice was 3.5 cm. in diameter. There was thickening and stiffening of the valve cusps, which were adherent to one another at the commissures. The aortic orifice was placed almost squarely above the septal defect, being only slightly more to the left than to the right.

The pulmonic valve was bicuspid, and adhesions between the two cusps had converted the valve into a funnel-like structure with the apex pointing distally. The diameter of the valve orifice was thus reduced to 1 cm. (Fig. 2). The cusps were thickened as well as adherent. The pulmonary artery itself was slightly narrowed.

There was localized thickening of the mitral valve along its line of closure, but this did not appear to be severe or extensive enough to impair the function of the valve materially.

Other lesions were chronic passive congestion of the organs in general; hypostatic hemorrhagic bronchopneumonia; central cirrhosis of the liver; old cholecystectomy; arteriosclerotic scarring of the kidneys; one recent renal infarct; subacute interstitial pancreatitis.

Fig. 1.—Septal defect.

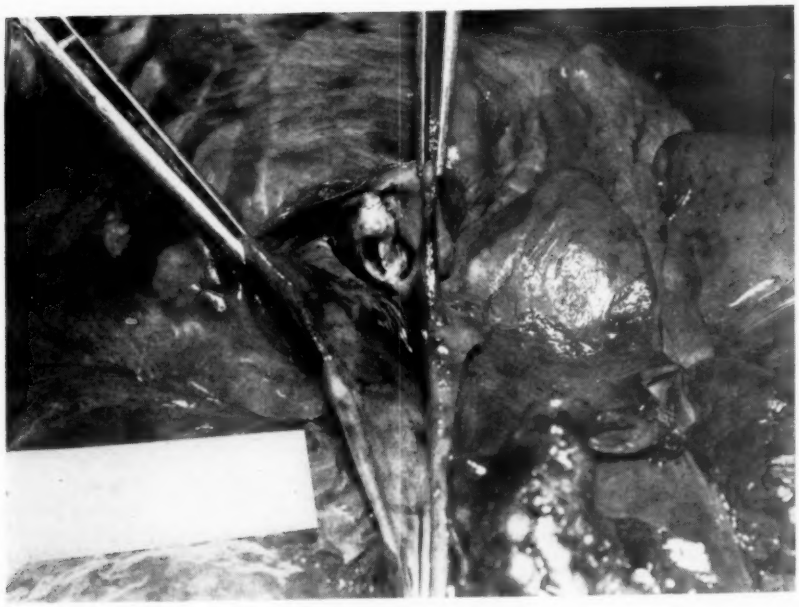

Fig. 2.—Pulmonic valve.

The findings in this patient, therefore, fulfilled the anatomic criteria of the classical tetralogy of Fallot. The additional clinical observation of pulmonic regurgitation was explained by the rigidity and incompetency of the bicuspid pulmonic valve.

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CARDIAC ASYSTOLE IN A NORMAL YOUNG MAN FOLLOWING PHYSICAL EFFORT

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THIS is the report of a cardiac asystole of nineteen seconds which occurred in a normal young soldier during a syncopal attack induced by physiologic means. Bradycardia during syncope is a common observation, and very low heart rates have been observed during syncopal attacks induced by various causes.[1-11] However, prolonged asystole during syncope is uncommon except in subjects with certain types of heart diseases or with carotid sinus sensitivity. In the present case syncope and asystole occurred while the subject was in the erect posture following a bout of hard physical work. Severe physical exertion has been shown to be frequently followed by an orthostatic hypotension[12-15] which may be so severe that syncope results.

The Harvard Pack Test[16] was used as the exercise procedure. The subject, stripped to shorts, socks, and shoes, and carrying a pack weighing one-third of his body weight, steps up and down on a platform sixteen inches high once every two seconds for five minutes. This work rate is of such severity that approximately one-third of normal young men fail to complete the required five minutes of effort. On stopping work, the subject sits down and, at intervals over the ensuing five minutes, the heart rate is counted. From these a fitness score is determined.

Following the five-minute sitting period, the subject in this study was placed on a tilt table which was used to change his posture alternately from 70 degrees erect to supine. While erect, the body weight was supported by the legs and no measures were taken to prevent postural sway, other than admonitions to stand still. Except when the erect periods were shortened by syncope, each position was maintained for five minutes during which the heart rate, blood pressure, respiratory rate, and electrocardiogram were repeatedly determined.

CASE REPORT

A white man, 22 years of age, weighing 165 pounds, and 5 feet, 8 inches in height, had completed basic training and for the preceding four months had engaged largely in clerical duties.

From the Armored Medical Research Laboratory, Fort Knox, Ky.
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Though somewhat overweight, his performance on fitness tests indicated an average physical fitness. The heart was not examined in detail but was assumed to be normal on the basis of good heart sounds without murmurs, a normal electrocardiogram, and the fact that he had passed several medical examinations without incident and had performed the physical tasks of military basic training without difficulty.

On Oct. 19, 1942, he performed the Harvard Pack Test, became exhausted after four minutes and ten seconds, and developed orthostatic hypotension with syncope in the postexertional standing periods. On Oct. 29, 1942, he performed the test for the second time. He had had a mild common cold for four days but felt quite well. After two minutes and thirty seconds of effort, he was stopped because he began to lag behind the required pace of one step-up per two seconds.

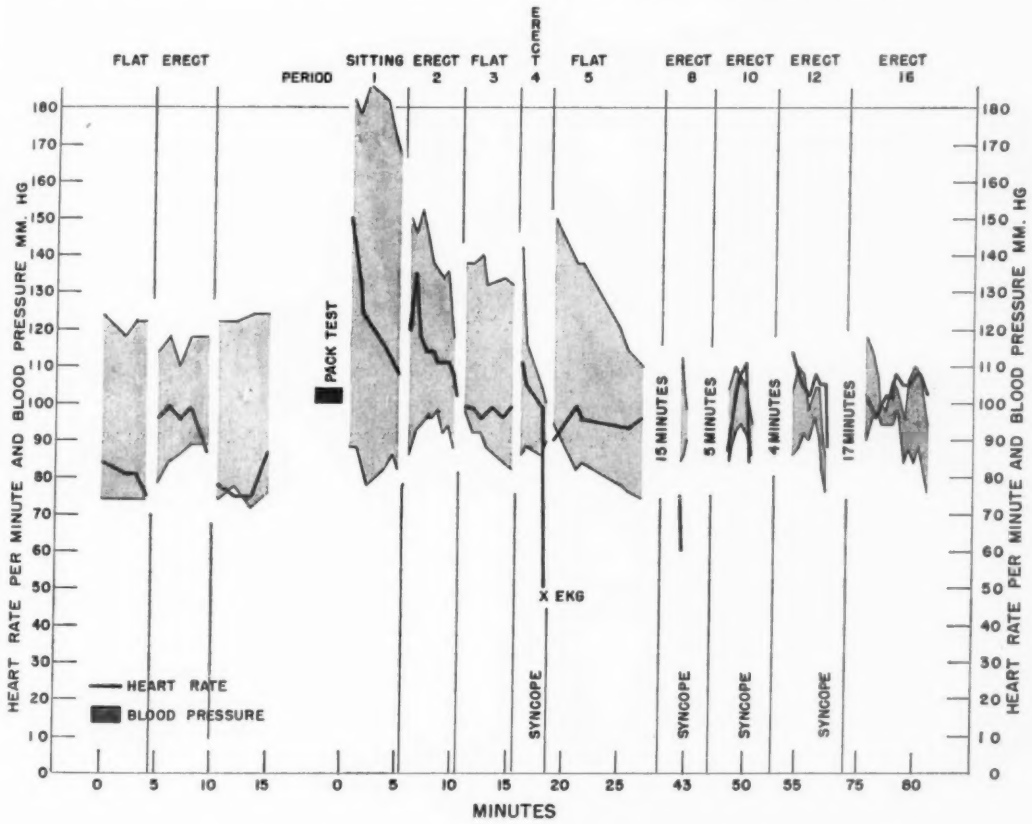

Fig. 1.—Response of blood pressure and heart rate to change of posture before and after severe physical effort (Harvard Pack Test). Heavy dark line, heart rate; shaded area, blood pressure. After Period 5, only the erect periods are plotted. Each of these was preceded and followed by a supine period in which the blood pressure and heart rate were similar to those at the end of Period 5.

Some of the circulatory changes induced by this second test are shown in Fig. 1. The elevated systolic blood pressure and rapid heart rate immediately after exercise (Period 1) are the usual results of physical work. Both the elevated blood pressure and heart rate subsided toward control values during the first erect period (Period 2) which was maintained for the required five minutes without discomfort. The breathlessness and distressing symptoms induced by the work had already disappeared. During the second erect period (Period 4) the systolic blood pressure

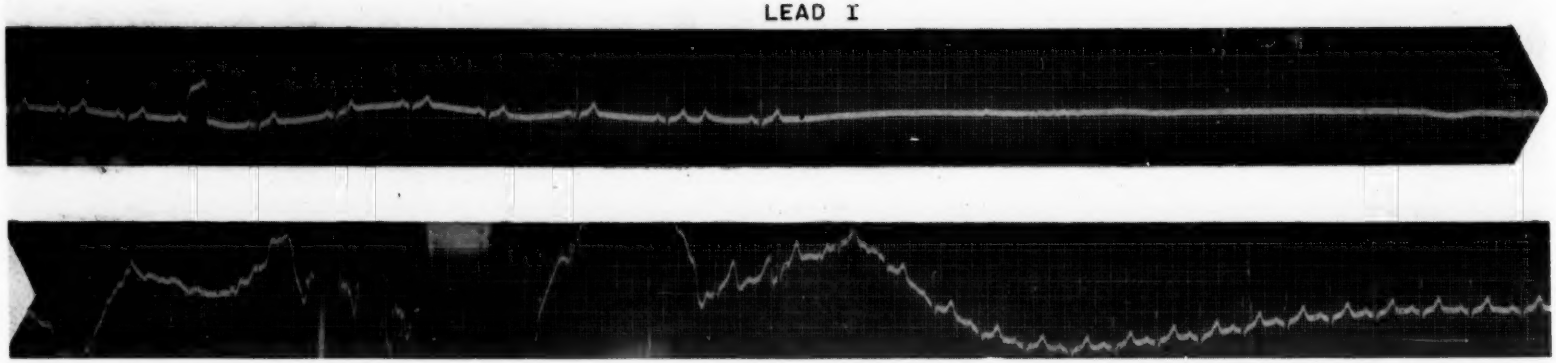

Fig. 2.—Electrocardiogram (Lead I) taken in the erect posture eighteen minutes after stopping work and at the time of collapse. The two strips form a continuous tracing; the lower one follows the upper one without a break in time. The apparent "wave" following the T wave of the next to the last complex in the upper strip is unexplained.

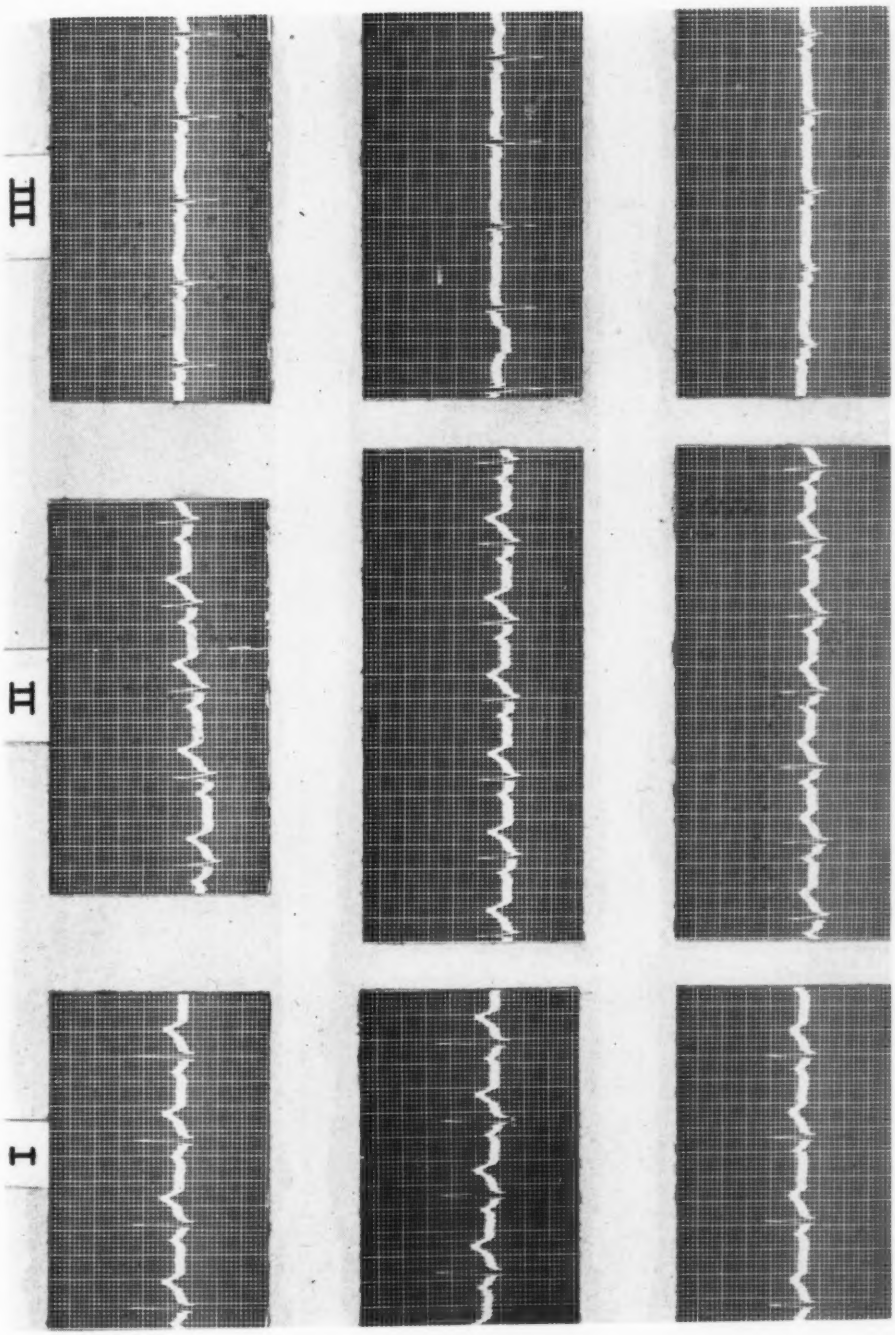

Fig. 3.—Control electrocardiograms before physical exertion. Upper tracings, subject supine; blood pressure, 122/74; heart rate, 87. Middle tracings, subject sitting; heart rate, 94. Lower tracings, subject erect; blood pressure, 118/88; heart rate, 100.

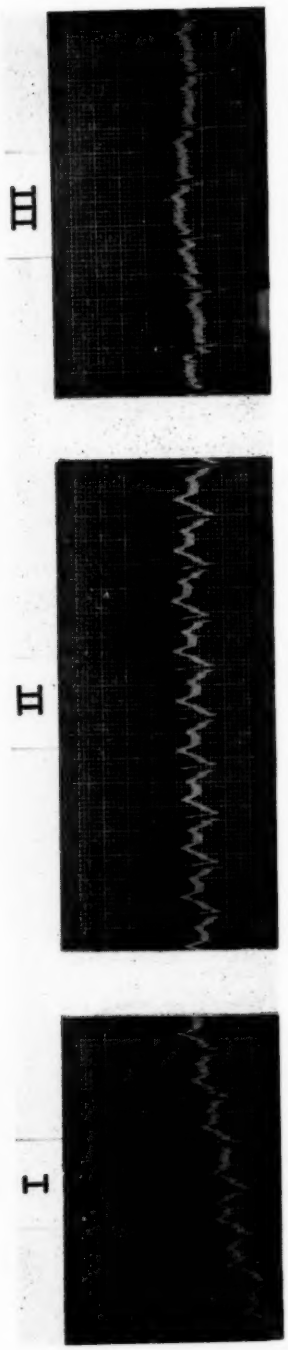

Fig. 4.—Electrocardiogram immediately after cessation of exercise. Subject seated; blood pressure, 182/88; heart rate, 150.

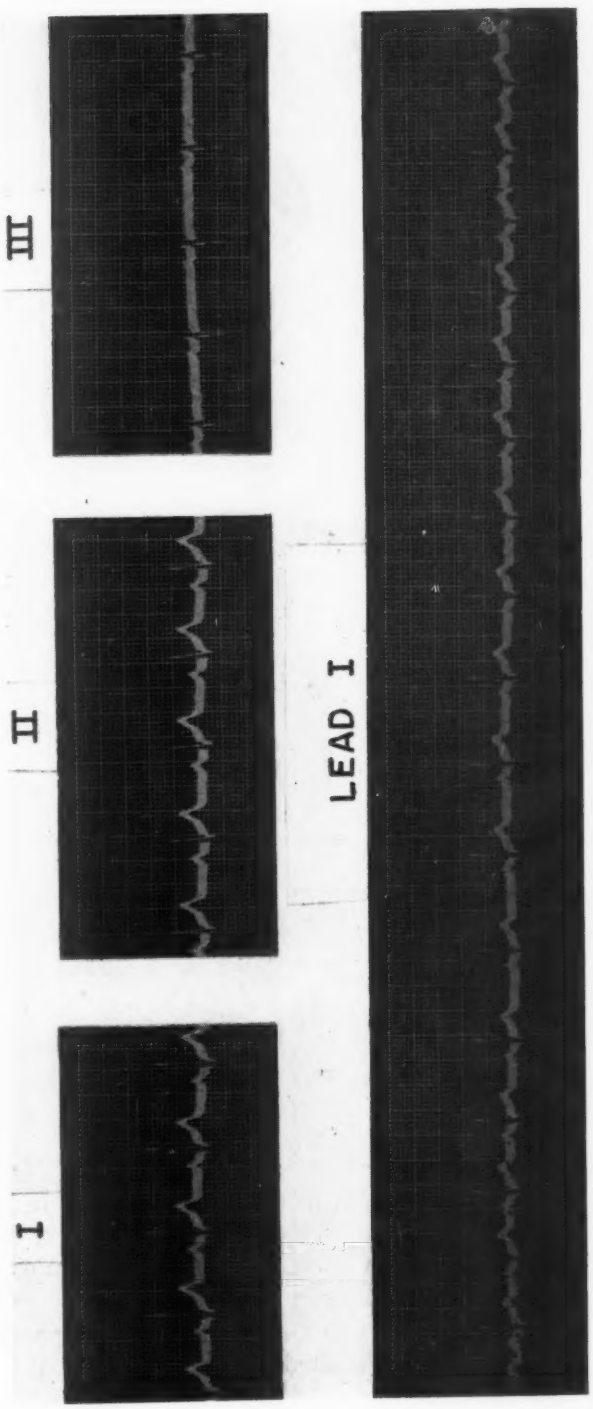

Fig. 5.—Upper tracing, electrocardiogram taken forty-five minutes after exertion. Subject supine, blood pressure, 108/76; heart rate, 90. Lower tracing, electrocardiogram (Lead I) taken in erect posture fifty-six minutes after exertion. Blood pressure, 100/92; heart rate, 105. Note transitory sinus slowing of cardiac rate in the middle of the tracing.

fell steadily, the diastolic blood pressure remained unchanged, and the pulse pressure narrowed markedly. The heart rate, instead of accelerating, slowed progressively. Signs of increasing discomfort and incipient syncope developed. After standing for two minutes and forty-five seconds of this period, the blood pressure was 100/90 and the heart rate, 99 per minute; the subject was in severe distress. Suddenly the heart rate slowed markedly and before the subject could be tilted flat, he lost consciousness, collapsed, and had a short clonic convulsion. After becoming supine, consciousness rapidly returned and, with it, apparently complete subjective recovery.

At the time of the collapse an electrocardiogram was being taken and is shown in Fig. 2. The two strips of this tracing are both Lead I and form a continuous record; the lower strip follows the upper one without a break in time. The tracing shows an increasing sinus bradycardia which leads to complete cardiac standstill. After 10.12 seconds of asystole (beginning of lower strip), the tracing is distorted by the muscular activity of the collapse and convulsion. A little over nineteen seconds (19.08) elapse between the onset of asystole and the first identifiable cardiac complex. This complex has a T wave of markedly increased amplitude which in subsequent complexes quickly reverts almost, but not quite, to the height of the pre-exercise control.

For comparison, pre-exercise control electrocardiograms in the supine, sitting, and 70 degree erect posture are shown (Fig. 3), as well as the tracing taken immediately (from thirty seconds to ninety seconds) after the cessation of work (Fig. 4).

Fig. 1 also shows that the postexertional orthostatic hypotension, syncope, and terminal bradycardia persisted for a considerable length of time. Syncope still occurred when the subject was upright, forty-three minutes (Period 8), fifty-one minutes (Period 10), and fifty-eight minutes (Period 12) after exertion. However, these periods showed a progressive improvement in the circulatory response to the erect posture. With each succeeding period the blood pressure was sustained for a progressively longer time before it suddenly fell and was accompanied by syncope and slowing of the heart rate. It was not until one hour and fifteen minutes after the cessation of exertion (Period 16) that the erect posture could be maintained for the required five minutes, and even then the circulatory response had not yet returned to normal. The widely fluctuating, often low, blood pressure and the markedly narrowed pulse pressure indicated a persisting circulatory instability.

Two electrocardiograms taken during this recovery period are shown in Fig. 5. The upper tracing, taken forty-five minutes after exertion and with the subject supine, is now similar to the pre-exercise control electrocardiogram. The lower tracing is Lead I taken fifty-six minutes after stopping work. The subject was erect; blood pressure, 100/92; pulse rate, 105 per minute. The transitory sinus slowing of the cardiac rate which appears in the middle of the tracing indicates that the conditions which produced the earlier asystole still persisted but to a very much milder degree.

DISCUSSION

The postexertional syncopal attack here described follows the pattern of vasovagal syncope described by Lewis.[17] The sudden cardiac slowing is generally attributed to vagal activity induced in turn by cerebral hypoxia. It has been demonstrated that marked vagal slowing of the heart occurs when the oxygen tension of the blood flowing to the brain is critically lowered[18,19] or when the volume of the blood flow to the brain is markedly reduced.[19,20] In the case here described the train of events is believed to have been as follows: hypotension produced deficient cerebral blood flow which resulted in cerebral hypoxia; the latter induced vagal stimulation of sufficient intensity to produce cardiac arrest.

The occurrence of asystole following physical exertion is reported largely because of its intrinsic interest. Here is a complete cardiac arrest induced by physiologic means. One speculates whether this episode may not have greater significance. Sudden death during or after exertion has been repeatedly encoun-

tered, even in apparently healthy young adults and athletes. Such deaths are usually attributed to a pathologic cardiac accident, generally coronary occlusion with myocardial infarction and terminal ventricular fibrillation. Where autopsy has been performed in such deaths, the overwhelming majority have revealed longstanding organic cardiac disease, often of a severe degree.[21-23] Occasionally no cardiac lesions are found. In both instances, *fresh* lesions capable of producing and explaining the immediate and sudden death are usually absent. This led Weiss[24] to call attention to the possibility that sudden death of this type might be the result not of an organic cardiac lesion but of purely circulatory changes, a "physiologic" death. He suggested a fatal vasovagal syncope. The present case demonstrates that cardiac arrest, presumably of vagal origin, can occur under certain circumstances following severe exertion and suggests that this phenomenon may persist for a considerable time after the cessation of effort. In a healthy youth, presumably with a good myocardium and coronary circulation, the heart and the subject recovered from the vagal arrest without apparent ill effect. Perhaps a heart involved by myocardial or coronary artery disease may not recover and death may ensue. Weiss has suggested that diseased hearts are more prone to reflex cardiac stimulation than normal hearts.

In the present case it is possible that the mild common cold may have played a significant role in the asystolic episode, for the circulation is known to be less stable during infections. Since fatality did not occur, this case cannot be regarded as indicating the mechanism of sudden death after exertion. For the same reason it cannot substantiate the hypothesis of fatal vasovagal syncope. It does, however, make this concept seem attractive.

SUMMARY

1. While standing erect following an episode of hard physical work, a normal young soldier suffered a syncopal attack during which a cardiac arrest for nineteen seconds occurred.

2. Such an asystole raises again the question whether sudden death during and after physical exertion may be the result of a fatal vasovagal syncope.

It is a pleasure to acknowledge the assistance of Major Edgar A. Blair, Infantry, Army of the United States, in this study, and the technical participation of Tec. 3 Howard Golden and Tec. 4 Wayland James.

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Abstracts and Reviews

Selected Abstracts

Herrmann, G. R.: Cholesterol Levels in Various Diseases and the Effects of Decholesterizing Agents. Texas State J. Med. **42**:260 (August), 1946.

Atherosclerosis, once established, has always been considered irreversible. The treatment usually recommended has been indirect or palliative. A definite relationship appears to exist between atheromatous vascular disease and cholesterol metabolism. It is suggested that in the presence of hypercholesterolemia and a permeable intima, small plaques may increase in size by a process of imbibition with the ultimate development of occluding atheromata or rupture with local thrombosis.

A study was made of 120 patients who had coronary thrombosis. This group exhibited high serum cholesterol which was 33 per cent above normal for total cholesterol and 26 per cent above normal for cholesterol esters. There was evidence to indicate that the lowering of the level of cholesterol in the plasma may facilitate the removal of this substance from plaques and reduce the abnormal cholesterol deposits in the vascular system. The possibility of accomplishing decholesterization of tissue deposits has been suggested by many authors. Lipotropic factors, such as pancreatic extracts, lipolysin, lipocaic, choline, and methionine, have been found to be effective in the treatment of fatty cirrhosis that results from a nutritional defect incident to alcoholism.

The authors studied the following regimes: (1) a low-fat diet with potassium iodide (in 13 patients); (2) thyroid extract in daily doses not exceeding 100 mg. (in 18 patients); (3) choline, 1.0 Gm. given three times daily (in 35 patients); (4) methionine, 0.5 Gm. given three times daily (in 4 patients); (5) Inositol, 0.5 Gm. given four times daily (in 9 patients); (6) Berenjena, a powder of Solanum Melongena L., 1 Gm. daily (in 4 patients); (7) Alcaucil, a powder of Cynara Scolymus, 1 Gm. given three times daily (in 10 patients).

The application of these measures resulted in varying degrees of reduction in the blood level of cholesterol and cholesterol esters. The lipotropic agents produced no disagreeable secondary effects. The patients, with few exceptions, reported that they felt better and that the frequency and severity of their precordial discomfort was reduced.

BELLET.

Melville, K. I.: The Protective Action of Atabrine Against Chloroform-Adrenaline Ventricular Fibrillation. J. Pharmacol. & Exper. Therap. **87**:350 (August), 1946.

The author had previously demonstrated the efficacy of coronary vasodilators in preventing the occurrence of ventricular fibrillation following injection of large doses of posterior pituitary extract in dogs under phenobarbital narcosis. In a previous communication he had also shown that atabrine was a powerful coronary vasodilator in the isolated perfused rabbit's heart. He therefore tested the effect of atabrine in preventing the development of ventricular fibrillation as a result of different procedures. The intravenous injection of atabrine was found to be capable of protecting dogs from ventricular fibrillation which follows the administration of chloroform

and adrenaline. This protective action also occurred after double vagotomy or atropinization. The effect of atabrine was found to be exceedingly transitory, even when quantities of the drug are injected slowly into the circulating blood. The data did not permit any definite conclusions concerning the mechanism of the phenomenon. The author suggests that it may depend upon the coronary-vasodilator action of atabrine. This action of atabrine might offset either an initial reduction in coronary flow or some impairment in myocardial nutrition induced by adrenaline under the conditions described. BELLET.

Farah, A.: Lethal Dose and Average Rate of Uptake of G-Strophanthin in the Heart-Lung Preparation of the Dog Under Varying Conditions. J. Pharmacol. & Exper. Therap. **87**:364 (August), 1946.

The author had previously shown that 1 gram of heart in the heart-lung preparation of the dog binds only one minimum lethal dose of g-Strophanthin, regardless of the rate of administration of the drug. In these earlier studies, certain experimental conditions, such as work of the heart, blood temperature, blood volume, and heart rate were kept constant.

The object of the present study was to see whether quantitative and qualitative changes in the work of the heart or changes of blood volume, temperature, or heart rate have any influence on the lethal dose, the minimal lethal dose, or average rate of uptake of g-strophanthin in the heart-lung preparation of the dog.

Reduction in the work of the left heart did not significantly influence either the lethal dose or minimal lethal dose of g-strophanthin. The average rate of uptake was also unchanged, irrespective of whether the work of the heart was high or low. A reduction in the blood volume led to a decrease of the lethal dose of g-strophanthin when high rates of administration were used. As the rate of administration was diminished, the lethal dose approached that determined with the higher blood volume. The reduction in the blood volume does not affect the minimum lethal dose of g-strophanthin although it changes the lethal dose. Reduction of the blood temperature increased the lethal dose and decreased the average rate of uptake and optimal rate of administration. The minimal lethal dose of g-strophanthin was not influenced by changes in the blood temperature from 35 to 39° C.

Sublethal doses of barium chloride and epinephrine did not change the lethal dose, the minimal lethal dose, or average rate of uptake of g-strophanthin in the heart-lung preparation of the dog. Caffein sodium benzoate increased the average rate of uptake but did not increase the minimal lethal dose of g-strophanthin. No differences in sensitivity to digitoxin could be detected between intact anesthetized pups and adult dogs. BELLET.

Dripps, R. D., and Deming, M. V. N.: An Evaluation of Certain Drugs Used to Maintain Blood Pressure During Spinal Anesthesia. Surg., Gynec. & Obst. **83**:312 (Sept.), 1946.

The vascular response of twenty-five hundred patients who received spinal anesthesia was studied. Five hundred patients received no pressor drug prior to anesthesia. In this group the average fall in systolic blood pressure was 36 per cent from the pre-operative level. Five hundred patients received paredrine for the purpose of maintaining blood pressure level. The average fall in this group was 18.6 per cent. Five hundred patients who were given ephedrine showed an average decrease in blood pressure of 14.5 per cent. Five hundred patients who received pitressin-ephedrine showed an average decrease of 5.3 per cent. Five hundred patients who were given methedrine showed a 3.0 per cent decrease in systolic blood pressure. Methedrine and pitressin-ephedrine were therefore the most effective of the drugs used. Methedrine is preferred to pitressin-ephedrine for a number of reasons. The former drug is administered intramuscularly in doses of 20 mg. at the time of lumbar puncture. The onset of action is prompt and the duration is prolonged.

The incidence and degree of the decrease in blood pressure which follows spinal anesthesia is greater with higher levels of anesthesia, in older individuals, and in patients whose initial blood pressures are above normal. There is no difference in vascular response when procaine and pontocaine are used as spinal anesthetic agents. NAIDE.

Warren, R.: War Wounds of Arteries. Arch. Surg. **53**:86 (July), 1946.

Experience with 115 patients with arterial wounds resulted in the following impressions. The critical arteries are the popliteal, the internal carotid, and the common femoral. Others become critical if the collateral circulation has been involved by the wound. Early ligation or ligation for secondary hemorrhage is dangerous. Late or elective ligation is much less so. The chief time for sympathectomy is before operative interruption of a critical artery. Its use as a prophylactic against spasm of collateral arterial supply is its most important function. If there is not time to do a sympathectomy before and this operation can be performed within six hours after such interruption, it is still indicated, but much less benefit can be expected. If sympathectomy is impossible, sympathetic block, repeated as often as practicable, should be used for forty-eight hours. The release from closed spaces, such as the popliteal space, of blood clots or edema through large incisions which are left open is of extreme importance in affording free flow through collateral vessels. In early cases of wounds of critical arteries, the use of venous grafts or prostheses is indicated. In the decision as to whether a graft or prosthesis should be used in a patient having a late or elective ligation, the one most important indication for their use is lack of good arterial back bleeding from the distal stump. A circular bandage should not be used on any limb that has a doubtful circulation. NAIDE.

Colby, F. H.: Venous Thrombosis and Pulmonary Emboli in Urology. J. Urol. **56**:124 (July), 1946.

The incidence of pulmonary embolism on the urologic service at the Massachusetts General Hospital is reported. A comparison is made of the incidence of pulmonary embolism in the years 1939 and 1940 with the incidence in 1943 and 1944. The purpose of the study was to determine whether early ambulation and femoral vein interruption had lessened the incidence of venous thrombosis, pulmonary infarction, and fatal pulmonary emboli. There were approximately one-third as many venous thromboses and pulmonary infarcts in 1943 and 1944, when early ambulation after operation was the rule and femoral vein interruption was practised, as there were in 1939 and 1940, when these measures were not applied. These measures reduced the incidence of fatal pulmonary emboli by two-thirds in the group of patients operated upon for prostatic obstruction. They failed, however, to eliminate these serious complications entirely or even to reduce them to such a degree as to allow the feeling that the patient was free of danger. Despite early ambulation, careful examination of the legs, and detection of small infarcts in the lungs by x-ray study, a mortality from pulmonary emboli of 0.93 per cent occurred in 1943 and 1944. In 1943 and 1944 there were nine bilateral vein interruptions performed on patients with prostatic obstruction. Six were for postoperative thromboses and infarcts and three were performed before prostatic surgery as a prophylactic measure. None of these three patients had fatal emboli. Femoral vein interruption as a prophylactic procedure is now being performed more frequently on selected patients. NAIDE.

Goodman, E. N., Messinger, W. J., and White, J. C.: Indications and Results of Surgery of the Autonomic Nervous System in Naval Personnel. Ann. Surg. **124**:204 (Aug.), 1946.

Raynaud's syndrome, hyperhydrosis, and hypertension are often encountered in unstable emotional individuals or in those having high vasomotor tone. The psychologic experiences of military life accentuate these phenomena and the transition from military to civilian life in turn may evoke similar responses.

Fifty-three patients are reported in whom preganglionic sympathectomy was performed for various peripheral vascular conditions and a more extensive sympathectomy for hypertension. The results obtained in Raynaud's syndrome, as well as in thromboangiitis obliterans, arteriosclerosis, and vasospasm, following wounds of major arteries, were uniformly good. Good results were also obtained in hyperhydrosis, in thrombophlebitic complications with vasospasm, and in painful states such as causalgia, certain amputation stump neuralgias, and angina pectoris. Conclusions concerning the effects of surgical intervention in hypertension are limited by the lack of long follow-up studies, but the immediate results on patients observed over a period of two years are significant lowering of blood pressure, relief of distressing headaches, nervousness, and irritability, and rehabilitation to useful occupations. No fatalities or serious complications have resulted from the operative procedures. NAIDE.

Hines, E. A., Jr., and Farber, E. M.: Ulcer of the Leg Due to Arteriosclerosis and Ischemia, Occurring in the Presence of Hypertensive Disease (Hypertensive-Ischemia Ulcers): A Preliminary Report. Proc. Staff Meet., Mayo Clin. **21**:337 (Sept. 4), 1946.

A series of eleven cases is reported in which leg ulcers were associated with hypertensive disease of long duration and considerable sclerosis of the retinal arterioles of the chronic hypertensive type. The authors postulate that changes similar to those in the retinal arterioles may also occur in the small arteries of the skin and subcutaneous tissues and give rise to small areas of infarction of the skin. As a result of trauma or for some unknown reason, the skin may break down with consequent formation of an ischemic ulcer. In only two of the eleven cases was there any evidence of occlusive disease in the larger arteries of the extremities. In these two cases the arterial pulsations were diminished but not absent, and no evidence of gross arterial insufficiency was found.

The ulcers were located on the lateral surface of the ankle or lower part of the leg and ranged in size from about 1 to 7 cm. in diameter. The ulcer usually had a purpuric base and in five cases was surrounded by a purpuric circle. The ulcers were usually superficial and had a rather punched-out appearance. The base appeared to be ischemic and granulation was not extensive. The ulcer was usually painful when fully developed. When healing finally began, it progressed slowly and from one to six months passed before the lesion healed entirely.

Histopathologic study of the ulcers and adjacent skin in five cases revealed organic changes in the arterioles. The most common changes were an increase in the thickness of the arteriolar wall and a decrease in the diameter of the lumen.

In none of the cases was there a history of thrombophlebitis. Furthermore, the lesions in this group were located in regions not commonly involved in chronic venous insufficiency; that is, on the lateral surface of the leg, in contrast to the usual location of stasis ulcers which is low on the medial surface of the leg.

In addition to chronic venous insufficiency, the following conditions should also be ruled out by pathologic study before the diagnosis of hypertensive ischemic ulcer is made: occlusive arterial disease, syphilis, blood dyscrasia, cutaneous sensitivity to drugs, frostbite, seasonal variations affecting the occurrence of the lesions, and serious local injury or other disease. NAIDE.

DeTakats, G., Graupner, G. W., Fowler, E. F., and Jensik, R. J.: Surgical Approach to Hypertension. Arch. Surg. **53**:111 (Aug.), 1946.

The results of the surgical treatment of hypertension, based on the pre-operative and post-operative study of fifty-two patients, are discussed in detail. For an improvement in the results of surgical treatment, a rigid selection of cases is advocated. The patients fall into three groups.

Group 1 includes patients who present a clear-cut indication for surgical treatment. There should be a persistent casual hypertension of over 140 systolic and 90 diastolic in persons between 18 and 25 years of age before operation is considered. Patients in Group 1 are predominantly asymptomatic and the hypertension is recognized at pre-employment, pre-induction, or insurance examinations. A distinction should be made between the hypertension of patients in Group 1 and the hypertension of adolescents who may come from hypertensive families and who, during

their period of growth when increased pluri-glandular function is increased, show an elevated pressure which may become normal in early adult life. For patients in Group 1, frequent re-examinations are advised at three-month intervals. No type of medical treatment seems effective in preventing the occurrence of typical juvenile hypertension. It is in this group, the members of which have minimal or no organic changes, that the best results were obtained by extensive sympathectomy. Of the seventeen patients in Group 1 who were operated upon, only two had recurrent hypertension which was corrected after completion of a technically incomplete operation.

Group 2 is one in which the indication for surgery is relative and debatable. This group consists of the middle-aged hypertensive patients who are beginning to show symptoms and evidence of organic damage. Twenty-four patients in this group were treated surgically. Of these, six showed recurrence of hypertension. These six were analyzed and found to have either striking enlargement and rigidity of the aorta or the continuous vasospasm of severe benign nephrosclerosis or pyelonephritis which must be regarded as the pre-malignant phase.

Group 3 consisted of ten patients with pre-malignant and malignant hypertension. These patients are not suitable for operation, despite the occasional spectacular results reported in the literature. The argument, frequently brought forward, that all other types of treatment have failed, and that the patient has nothing to lose since his prognosis is so poor, is not a valid one; operation in this series has been found to be useless in this type of patient.

This study also does not bear out the observation of other investigators that a marked drop in blood pressure with high spinal anesthesis denotes that a good result can be expected from extensive sympathectomy. In operating on a large number of older arteriosclerotic patients with hypertension under spinal anesthesia, severe fall in blood pressure has been repeatedly observed. Such patients, however, could hardly be regarded as suitable for sympathectomy.

Patients with pyelonephritis, post-toxemic hypertension, streptococcic nephritis, and rheumatic reno-vascular damage are favorable candidates for surgery, provided the vascular damage is not too far advanced. On the other hand, the "neurogenic" group has not done well. The fluctuations of their pressures have not been abolished and their emotional hypothalamic "outbursts" are not eliminated and continue to operate upon the vascular system.

The value of renal biopsies is discussed and also the help afforded by special post-operative studies including roentgenograms of the chest, electrocardiograms, tests of epinephrine sensitivity, and estimates of circulation time. The redistribution of circulation due to the effect of splanchnic nerve section on blood depots is stressed. So far, no single or combined method of treatment can be recognized which gives rigidily selected patients with hypertension as much benefit as the transdiaphragmatic splanchnic nerve section combined with dorsolumbar sympathetic ganglionectomy. NAIDE.

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THE American Heart Association was founded in 1924 "for the study of and the dissemination and application of knowledge concerning the causes, treatment and prevention of heart disease; the gathering of information on heart disease; the development and application of measures that would prevent heart disease; seeking and provision of occupations suitable for heart disease patients; the promotion of the establishment of special dispensary classes for heart disease patients; the extension of opportunities for adequate care of cardiac convalescents; the promotion of permanent institutional care for such cardiac patients as are hopelessly incapacitated from self-support; and the encouragement and establishment of local associations with similar objects throughout the United States."

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The American Council on Rheumatic Fever, organized in 1944, consists of a group of representatives of all national medical organizations concerned with rheumatic fever. It operates administratively through the American Heart Association and carries out the program of the American Heart Association insofar as that relates to rheumatic fever.

Annual membership in the American Heart Association is $2.50 and includes twelve issues of *Modern Concepts of Cardiovascular Disease;* Journal membership is $10.00 and includes a year's subscription to the American Heart Journal (January-December), twelve issues of *Modern Concepts of Cardiovascular Disease*, and annual membership in the Association. Contributing membership starts at $25.00 per year; patron membership is $50.00 and over per year. Membership blanks will be sent upon request.

The Association earnestly solicits your support and suggestions for its work. Donations will be gratefully received and promptly acknowledged.

ANNUAL MEETING

The Annual Meeting and Twentieth Scientific Sessions of the American Heart Association will be held in Atlantic City, N. J., June 6 and 7, 1947. The Hotel President will be the headquarters for all meetings. On June 6, a meeting will be held with representatives of local Heart Associations to discuss the administrative structure of the American Heart Association with particular reference to program. The annual meeting of members will also be held on that day. The scientific sessions will take place on June 6 and 7. The annual dinner is scheduled for Saturday evening, June 7, at the Hotel President. Meetings begin at 9:00 A.M. each day, and members should plan to arrive on June 5. Hotel rooms will be in great demand and every member who wishes to attend is urged to make reservations immediately.

The chairman of the Program Committee for the Annual Scientific Sessions of the American Heart Association is Dr. Edgar V. Allen, Mayo Clinic, Rochester, Minn. All who desire to present papers at the meetings of June 6 and 7 in Atlantic City should forward to him an abstract of the proposed presentation of not more than 300 words. The deadline for the receipt of abstracts is March 30, 1947.